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Dated 4 September 2003

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1. Your reference

PC25485

2. Patent application number
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0225908.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

Patents ADP number *(if you know it)*

6892673001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

TREATMENT OF FEMALE SEXUAL DYSFUNCTION

5. Name of your agent *(if you have one)*

Dr. B. Peter

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

UK Patent Department
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)*

8042160002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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Continuation sheets of this form	
Description	20
Claim *(s)*	3
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	Appendix 1 (PCS22026SMC-PROV) 146 pages ✓

11. I/We request the grant of a patent on the basis of this application.

Signature B. Peter B. Peter — Date 6th November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom — Dr. B. Peter — 01304.645854

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TREATMENT OF FEMALE SEXUAL DYSFUNCTION

FIELD OF INVENTION

The present invention relates the use of α_{1A} and/or α_{1L} adrenergic receptor antagonists for the treatment of female sexual dysfunction (FSD), in particular female sexual arousal disorder (FSAD) and/or female orgasmic disorder (FOD).

The present invention also relates to a method of treatment of FSD, in particular FSAD and/or FOD.

The present invention also relates to assays to screen for compounds useful in the treatment of FSD, in particular FSAD and/or FOD.

FEMALE SEXUAL RESPONSE

The female sexual response phase of arousal is not easily distinguished from the phase of desire until physiological changes begin to take place in the vagina and clitoris as well as other sexual organs. Sexual excitement and pleasure are accompanied by a combination of vascular and neuromuscular events which lead to engorgement of the clitoris, labia and vaginal wall, increased vaginal lubrication and dilatation of the vaginal lumen (Levin,R.J. (1980) Clin. Obstet. Gynecol. 7, 213-252; Ottesen, B. et al (1983) Eur. J. Clin. Invest. 13, 321-324; Levin, R.J. (1991) Exp. Clin. Endocrinol. 98, 61-69; Levin, R.J. (1992) Annu. Rev. Sex Res. 3, 1-48; Sjoberg,I (1992) Acta Obst. Gynecol. Scand 71, 84-85; Wagner, G. (1992) Sem. Neurol 12, 87-97; Schiavi *et al.* (1995) Psychiat. Clin. North Am. 18, 7-23; Berman, J.R. *et al.* (1999) Urology 54, 385-391).

Vaginal engorgement enables transudation to occur and this process is responsible for increased vaginal lubrication. Transudation allows a flow of plasma through the epithelium and onto the vaginal surface, the driving force for which is increased blood flow in the vaginal capillary bed during the aroused state. In addition engorgement leads to an increase in vaginal length and luminal diameter, especially in the distal 2/3 of the vaginal canal. The luminal dilatation of the vagina is due to a combination of smooth muscle relaxation of its wall and skeletal muscle relaxation of the pelvic floor muscles. Some sexual pain disorders such as vaginismus are thought to be due, at least in part,

to inadequate relaxation preventing dilatation of the vagina; it has yet to be ascertained if this is primarily a smooth or skeletal muscle problem.

The vasculature and micro vasculature of the vagina are innervated by nerves containing neuropeptides and other neurotransmitter candidates. These include calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY), nitric oxide synthase (NOS), substance P and vasoactive intestinal peptide (VIP) (Hoyle *et al.*, 1996). Peptides that are present in the clitoris are discussed *infra*. Nitric oxide synthase, which is often colocalised with VIP, displays a greater expression, immunologically, in the deep arteries and veins rather than in the blood vessels of the propria (Hoyle, C.H.V. *et al.* (1996) J. Anat. 188, 633-644).

FEMALE SEXUAL DYSFUNCTION

It is known that some individuals can suffer from female sexual dysfunction (FSD). Studies investigating sexual dysfunction in couples reveals that up to 76% of women have complaints of sexual dysfunction and that 30-50% of women in the USA experience FSD.

FSD is best defined as the difficulty or inability of a woman to find satisfaction in sexual expression. FSD is a collective term for several diverse female sexual disorders (Basson *et al* (2000) J. Urol. 163, 888-893). The woman may have lack of desire, difficulty with arousal or orgasm, pain with intercourse or a combination of these problems. Several types of disease, medications, injuries or psychological problems can cause FSD. Sub-types of FSD include hypoactive sexual desire disorder, female sexual arousal disorder (FSAD), female orgasmic disorder (FOD) and sexual desire disorder.

Treatments in development are targeted to treat specific subtypes of FSD, predominantly desire and arousal disorders.

The categories of FSD are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (Leiblum, S.R. (1998) Int. J. Impotence Res. 10, S104-S106). Desire or libido is the drive for sexual expression – and manifestations often include sexual thoughts either when in the company of an interested partner or when exposed to other erotic stimuli. In contrast, sexual arousal is the vascular response to sexual stimulation, an important component of which is vaginal lubrication and elongation of the vagina. Thus, sexual arousal, in contrast to sexual

desire, is a response relating to genital (e.g. vaginal and clitoral) blood flow and not necessarily sensitivity. Orgasm is the release of sexual tension that has culminated during arousal. Hence, FSD typically occurs when a woman has an inadequate or unsatisfactory response in any of these phases, usually desire, arousal or orgasm. FSD categories include hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorders and sexual pain disorders.

Hypoactive sexual desire disorder is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due either to natural menopause or to surgical menopause. Other causes include illness, medications, fatigue, depression and anxiety.

Female sexual arousal disorder (FSAD) is characterised by inadequate genital response to sexual stimulation. The genitalia (e.g. the vagina and/or the clitoris) do not undergo the engorgement that characterises normal sexual arousal. The vaginal walls are poorly lubricated, so that intercourse is painful. Orgasms may be impeded. Arousal disorder can be caused by reduced oestrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and atherosclerosis. Other causes result from treatment with diuretics, antihistamines, antidepressants eg SSRIs or antihypertensive agents. FSAD is discussed in more detail *infra*.

Sexual pain disorders (which include dyspareunia and vaginismus) are characterised by pain resulting from penetration and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

The prevalence of FSD is difficult to gauge because the term covers several types of problem, some of which are difficult to measure, and because the interest in treating FSD is relatively recent. Many women's sexual problems are associated either directly with the female ageing process or with chronic illnesses such as diabetes and hypertension. Numerous studies have also shown that between 11-48% of women overall may have reduced sexual desire with age. Similarly, between 11-50% of women report problems with arousal and lubrication, and therefore experience pain with intercourse. Vaginismus is far less common, affecting approximately 1% of women.

Because FSD consists of several subtypes that express symptoms in separate phases of the sexual response cycle, there is not a single therapy. Current treatment of FSD focuses principally on psychological or relationship issues. Treatment of FSD is gradually evolving as more clinical and basic science studies are dedicated to the investigation of this medical problem. Female sexual complaints are not all psychological in pathophysiology, especially for those individuals who may have a component of vasculogenic dysfunction (eg FSAD) contributing to the overall female sexual complaint. There are at present no drugs licensed for the treatment of FSD. Empirical drug therapy includes oestrogen administration (topically or as hormone replacement therapy), androgens or mood-altering drugs such as buspirone or trazodone. These treatment options are often unsatisfactory due to low efficacy or unacceptable side effects.

Since interest is relatively recent in treating FSD pharmacologically, therapy consists of the following:- psychological counselling, over-the-counter sexual lubricants, and investigational candidates, including drugs approved for other conditions. These medications consist of hormonal agents, either testosterone or combinations of oestrogen and testosterone and more recently vascular drugs, that have proved effective in male erectile dysfunction. None of these agents has been approved for the treatment of FSD.

FEMALE SEXUAL AROUSAL DISORDER (FSAD)

The sexual arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion and swelling of the external genitalia. The disorder causes marked distress and/or interpersonal difficulty. Studies investigating sexual dysfunction in couples reveals that there is a large number of females who suffer from sexual arousal dysfunction; otherwise known as female sexual arousal disorder (FSAD).

The Diagnostic and Statistical Manual (DSM) IV of the American Psychiatric Association defines Female Sexual Arousal Disorder (FSAD) as being: "a persistent or recurrent inability to attain or to maintain until completion of the sexual activity adequate lubrication-swelling response of sexual excitement. The disturbance must cause marked distress or interpersonal difficulty."

FSAD is a highly prevalent sexual disorder affecting pre-, peri- and post-menopausal (±HRT) women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and UG disorders.

The primary consequences of FSAD are lack of engorgement/swelling, lack of lubrication and lack of pleasurable genital sensation. The secondary consequences of FSAD are reduced sexual desire, pain during intercourse and difficulty in achieving an orgasm.

It has recently been hypothesised that there is a vascular basis for at least a proportion of patients with symptoms of FSAD (Goldstein, I & Berman, J.R (1998) Int. J. Impotence Res. 10, S84-S90) with animal data supporting this view (Park, K. *et al.* (1997) Int. J. Impotence Res. 9, 27-37).

Drug candidates for treating FSAD, which are under investigation for efficacy, are primarily erectile dysfunction therapies that promote circulation to the male genitalia. They consist of two types of formulation, oral or sublingual medications (Apomorphine, Phentolamine, Sildenafil), and prostaglandin (PGE_1 - Alprostadil) that are injected or administered transurethrally in men, and topically to the genitalia in women.

Phentolamine mesylate is a combined α_1 and α_2 adrenergic receptor antagonist, which was originally approved for the treatment of pheochromocytoma-induced hypertension and norepinephrine-related dermal necrosis. Since the early 1980s, it has been used in combination with other agents for intracavernosal injection therapy of erectile dysfunction, and more recently, an oral formulation of phentolamine was developed for treatment of mild or psychogenic erectile dysfunction. A small pilot study showed that the drug appeared to lead to mild improvements in FSAD (Rosen, R.C. et al (1999) J. Sex Marital Therapy 25, 137-144). A recent study identified that functional α_1 and α_2 adrenergic receptors are expressed on rabbit vagina (Kim et al (2002) Life Sciences 71, 2909-2920), and demonstrated that α adrenergic receptor antagonists can increase blood flow to the vagina and therefore may have potential as pharmacotherapeutic agents in treating some symptoms associated with FSAD.

There are three distinct α_2 adrenergic receptor subtypes, called α_{2A}, α_{2B}, and α_{2C}, which generally have a critical role in regulating neurotransmitter release from sympathetic nerves and from adrenergic neurons in the central nervous system.

A main function of α_1-adrenergic receptors (α_1 receptors) is to activate mitogenic responses and regulate growth and proliferation of many cells as well as being involved in mediating the contraction of vascular smooth muscle. There are 3 cloned α_1 receptor subtypes, α_{1A}, α_{1B}, and α_{1D}, all of which signal through the $G_{q/11}$ family of G-proteins, and different subtypes show different patterns of activation.

Although cloning studies suggest that all subtypes of α_1 receptors have been identified at the molecular level, it has been demonstrated that the α_1 receptor subtype mainly found in human prostate displays a different pharmacology to the cloned subtypes, and the receptor has been termed α_{1L} to reflect this fact. Tissue distribution studies of the cloned α_1 receptor subtypes suggest that α_{1A} is expressed in the human prostate, and the assumption is therefore that the α_{1L} receptor corresponds to α_{1A} molecularly, but is a different receptor at the functional level, possibly influenced by other factors (for example, the lipid composition in the membrane, or formation of complexes with other proteins or itself) to display the α_{1L} pharmacology (Daniels, D.V. et al (1999) Eur. J. Pharmacol. 370, 337-343).

Surprisingly, we have found that α_{1A} and/or α_{1L} antagonists, preferably selective α_{1A} and/or α_{1L} antagonists, originally developed for treatment of benign prostatic hyperplasia (BPH), are also advantageous in treating FSD, preferably FSAD and/or FOD. In addition to increasing vaginal blood flow they may also restore sexual arousal, increase vaginal lubrication, enhance vaginal and clittoral sensitivity, and therefore enhance orgasmic function.

The present invention therefore seeks to provide an effective means of treating FSD, and in particular FSAD and/or FOD, by using α_{1A} or α_{1L} antagonists, preferably selective α_{1A} or α_{1L} antagonists, alone or in combination with other agents.

Aspects of th Invention

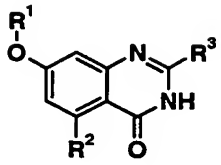
A seminal finding of the present invention is the ability to treat a female suffering from female sexual dysfunction (FSD), preferably female sexual arrousal disorder (FSAD) and/or female orgasmic disorder (FOD) with an antagonist for α_{1A} and/or α_{1L} adrenergic receptors. If the female to be treated is postmenopausal, she will preferably be on hormone replacement therapy (HRT), even more preferably she will also receive androgen therapy.

Therefore the invention relates to α_{1A} and/or α_{1L} receptor antagonists for use in the treatment of FSD, preferably FSAD and/or FOD. The invention also relates to the use of α_{1A} and/or α_{1L} adrenergic receptor antagonists for the manufacture of a medicament for the treatment of FSD, preferably FSAD and/or FOD. The invention also relates to a method of treatment of FSD, preferably FSAD and/or FOD, with an α_{1A} and/or α_{1L} adrenergic receptor antagonist. One aspect of the invention is therefore a method of treating FSD, preferably FSAD and/or FOD, comprising the administration to a patient in need of such treatment of an effective amount of an α_{1A} or an α_{1L} antagonist.

The α_{1A} and/or α_{1L} adrenergic receptor antagonists preferably will have an IC_{50} in a functional assay of less than 100nM, more preferably an IC_{50} of less than 10nM, even more preferably an IC_{50} of less than 1nM. The IC_{50} may be measured in a functional assay measuring contractile responses in rabbit aorta or human prostate for α_{1L} receptors, or rat vas deferens for α_{1A} receptors (see, for example, Example 3).

Preferably the α_{1A} and/or α_{1L} adrenergic receptor antagonists will be at least 10 fold selective over α_{1B}, more preferably at least 100 fold selective over α_{1B}. Preferably the α_{1A} and/or α_{1L} adrenergic receptor antagonists will be at least 10 fold selective over α_{1D}, more preferably at least 100 fold selective over α_{1D}. More preferably, the α_{1A} and/or α_{1L} adrenergic receptor antagonists will be at least 10 fold selective over α_{1B} and at least 10 fold selective over α_{1D}, most preferably at least 100 fold selective over α_{1B} and at least 100 fold selective over α_{1D}.

Suitable α_{1A} and/or α_{1L} antagonists include a compound of formula (I), as disclosed in GB Patent Application No: 0206033.3 (attached as Appendix 1 to this application):



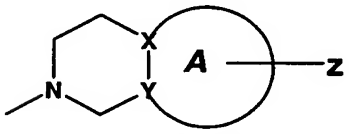
(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents C_{1-4} alkyl;

R^2 represents C_{3-6} cycloalkyl;

R^3 represents a bicyclic group of the formula



wherein X and Y are selected from C and N, provided that at least one is C;

Ring A together with X and Y represents a 5- or 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms in the ring;

Z is selected from H, and LR^4;

L represents a direct link, C_{1-4} alkylene or C_{1-4} alkoxyalkylene;

R^4 represents H, NR^5R^6, C_{3-6} cycloalkyl, OR^7 or Het^1;

R^5 and R^6 are independently selected from H, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with OR^8;

R^7 is selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{3-6}cycloalkyl, Het^2 and C_{1-4}alkyl-Het^3;

R^8 is H or C_{1-4} alkyl;

Het^1, Het^2 and Het^3 independently represent a 4 to 7 membered saturated heterocyclic group which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, O or S, optionally substituted with OR^9 and/or C_{1-4} alkyl optionally substituted by OR^9;

R^9 is H or C_{1-4} alkyl.

Preferably, suitable α_{1A} and/or α_{1L} antagonists are compounds exemplified in GB Patent Application No: 0206033.3 (attached as Appendix 1 to this application), more preferably one of the following compounds:

5-cyclopropyl-7-methoxy-2-(2-([dimethylamino]methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(1-pyrrolidinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-([dimethylamino]methyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-pyrrolidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-piperidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(4-morpholinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro[1,6]naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone or pharmaceutically acceptable salts or solvates thereof.

Suitable α_{1A} and/or α_{1L} receptor antagonists also include compounds included in patent application WO 98/30560, preferably the compounds exemplified in WO 98/30560, even more preferably 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, preferably a pharmaceutically acceptable salt or solvate thereof, most preferably the mesylate salt thereof.

Suitable α_{1A} and/or α_{1L} antagonists can also be found in patent application WO 02/053558. Another suitable α_{1A} and/or α_{1L} antagonist may be KMD-3213 (Drugs of the Future (2001) 26, 553-560.

For the sake of clarity, a compound can combine high potency for both α_{1A} and α_{1L} adrenergic receptor, and the use of such a compound for the manufacture of a medicament for the treatment of FSD, in particular FSAD and/or FOD, is within the scope of the invention.

The invention relates to the use of an α_{1A} and/or α_{1L} adrenergic receptor antagonist for the treatment of FSD, preferably FSAD and/or FOD, alone, or in combination with one or more other agents such as

- a phosphodiesterase (PDE) inhibitor, preferably a PDE5 inhibitor, such as sildenafil, or a PDE2 inhibitor, or
- a neutral endopeptidase (NEP) inhibitor, such as compounds FV to FXI and F57 to F65 of EP1097719-A1, or
- a central melanocortin agonist, preferably an MC-4 receptor agonist such as melanotan II, PT-14, or PT-141, or
- a dopamine receptor agonist, preferably a selective D3 receptor agonist, such as compounds disclosed in EP 0 899 267, or
- a neuropeptide Y (NPY) antagonist. e.g. as disclosed in WO-00/66578.

Preferably the patient will also be receiving Hormone Replacement Therapy (HRT), even more preferably HRT and additional androgen therapy. Agents used may include estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA) (i.e. as a combination), or estrogen and methyl testosterone hormone replacement therapy agent (e.g. HRT especially Premarin, Cenestin, Oestrofeminal, Equin, Estrace, Estrofem, Elleste Solo, Estring, Eastraderm TTS, Eastraderm Matrix, Dermestril, Premphase, Preempro, Prempak, Premique, Estratest, Estratest HS, Tibolone). Agents for androgen therapy include testosterone replacement agent (including dehydroandrostendione), testosternone (Tostrelle), dihydrotestosterone or a testosterone implant.

Reference to an antagonist, an agonist or an inhibitor shall at all times be understood to include all active forms of such agents, including the free form thereof (e.g. the free and/or base form) and also all pharmaceutically acceptable salts, polymorphs, hydrates, silicates, stereo-isomers (e.g. diastereoisomers and enantiomers) and so forth. Active metabolites of any of the compounds, in any form, are also included.

Particular formulations of the compounds for either oral delivery or for topical application (creams, gels) are included in the invention. An intravaginal formulation comprising a compound or combination of compounds as defined herein, preferably a formulation which is a creme or a gel, is also included in the invention.

A method of enhancing sexual function of a female comprising administering an α_{1A} and/or an α_{1L} antagonist to a healthy female is a further aspect of the invention.

Yet a further aspect of the invention is a method of screening for compounds useful for treating FSD, preferably FSAD and/or FOD, comprising screening compounds for antagonist activity against α_{1A} and/or α_{1L} adrenergic receptor and selecting compounds with an IC_{50} of less than 100nM, preferably with an IC_{50} of less than 10nM, even more preferably with an IC_{50} of less than 1nM.

"Potency" as used herein is a measure of the concentration of a compound at which it is effective. The potency of a compound can be determined in a binding assay as described in Example 2, and potency in this context will refer to the IC_{50} of the compound, i.e. to the concentration inhibiting 50% of the labelled compound from binding to the receptors. The potency of a compound can also be determined in a functional assay such as contractile assays for different tissues expressing different α_1 receptor subtypes as described in Example 3. The potency in this case would refer to the IC_{50} of the compound, i.e. the concentration which inhibits 50% of the functional response seen by application of the agonist.

"Selectivity" as used herein is a measure of the relative potency of a drug between two receptor subtypes for the same endogenous ligand. This can be determined in binding assays as described in Example 2, or in functional assays as described in Example 3.

Example 1: Assay to show beneficial effects of compounds and combination of compounds in FSAD

(a) Anaesthetic Protocol

Female New Zealand rabbits (~2.5kg) were pre-medicated with a combination of Medetomidine (Domitor®) 0.5ml/kg *i.m.*, and Ketamine (Vetalar®) 0.25ml/kg *i.m.* whilst maintaining oxygen intake via a face mask. The rabbits were tracheotomised using a Portex™ uncuffed endotracheal tube 3 ID (internal diameter), connected to ventilator and maintained at a ventilation rate of 30-40 breaths per minute, with an approximate tidal volume of 18-20 ml, and a maximum airway pressure of 10 cm H_2O. Anaesthesia was then switched to Isoflurane and ventilation continued with O_2 at 2l/min. The right marginal ear vein was cannulated using a 23G or 24G catheter, and Lactated Ringer solution perfused at 0.5ml/min. The rabbit was maintained at 3% Isoflurane during invasive surgery, dropping to 2% for maintenance anaesthesia.

(b) Cannulation of Vessels

The left groin area of the rabbit was shaved and a vertical incision was made approximately 5cm in length along the thigh. The femoral vein was exposed, isolated and then cannulated with a PVC catheter (17G) for the infusion of drugs and compounds. Cannulation was repeated for the femoral artery, inserting the catheter to a depth of 10cm to ensure that the catheter reached the abdominal aorta. This arterial catheter was linked to a Gould system to record blood pressure. Samples for blood gas analysis were also taken via the arterial catheter. Systolic and diastolic pressures were measured, and the mean arterial pressure calculated using the formula (diastolic x2 + systolic) ÷3. Heart rate was measured via the pulse oxymeter and *Po-ne-mah* data acquisition software system (Ponemah Physiology Platform, Gould Instrument Systems Inc).

(c) Stimulation of the Pelvic Nerve

A ventral midline incision was made into the abdominal cavity. The incision was about 5cm in length just above the pubis. The fat and muscle was *bluntly* dissected away to reveal the hypogastric nerve which runs down the body cavity. It was essential to keep close to the side curve of the pubis wall in order to avoid damaging the femoral vein and artery which lie above the pubis. The sciatic and pelvic nerves lie deeper and were located after further dissection on the dorsal side of the rabbit. Once the sciatic nerve was identified, the pelvic nerve was easily located. The term *pelvic nerve* is loosely applied; anatomy books on the subject fail to identify the nerves in sufficient detail. The

pelvic nerve is known to innervate the female genitalia and it is documented that stimulation of the pelvic nerve causes an increase in genital blood flow. Hence we are confident that the nerve we are stimulating in this study is the pelvic nerve. Confidence levels are based on 1./ upon stimulation we observe an increase in vaginal and clitoral blood flow, and 2./ we have traced the passage of the nerve from the female genitalia, through the pelvic ganglion back to it's spinal origin in the S2/S4 region. The pelvic nerve was freed away from surrounding tissue and a *Harvard* bipolar stimulating electrode was placed around the nerve. The pelvic nerve was slightly lifted to give some tension, then the electrode was secured in position. Approximately 1ml of light paraffin oil was placed around the pelvic nerve and electrode. This acts as a protective lubricant to the pelvic nerve and prevents blood contamination of the electrode. The electrode was connected to a *Grass* S88 Stimulator. The pelvic nerve was stimulated using the following parameters:- 5V, pulse width 0.5ms, duration of stimulus 10 seconds and a frequency range of 2 to 16Hz. Reproducible responses were obtained when the nerve was stimulated every 15 minutes.

A frequency response curve was determined at the start of each experiment in order to determine the optimum frequency to use as a sub-maximal response, normally 4Hz. The compound(s) to be tested were infused, via the femoral vein, using a *Harvard* 22 infusion pump allowing a continuous stimulation cycle every 15 minutes.

(d) Positioning of the Laser Doppler Probes

A ventral midline incision was made, at the caudal end of the pubis, to expose the pubic area. Connective tissue was removed to expose the tunica of the clitoris, ensuring that the wall was free from small blood vessels. The external vaginal wall was also exposed by removing any connective tissue. One laser Doppler flow probe was inserted 3cm into the vagina, so that half the probe shaft was still visible. A second probe was positioned so that it lay just above the external clitoral wall. The position of these probes was then adjusted until a signal was obtained. Both probes were clamped in position.

Vaginal and clitoral blood flow was recorded either as numbers directly from the Flowmeter using *Po-ne-mah* data acquisition software (Ponemah Physiology Platform, Gould Instrument Systems Inc), or indirectly from Gould chart recorder trace. Calibration was set at the beginning of the experiment (0-125ml/min/100g tissue).

( ) Infusion of Vasoactive Intestinal Polypeptide (VIP)

The doses of VIP (Bachem, H-3775) infused were 6.0, 20.0, 60.0 μg/kg *iv.* and were infused in a volume of 1.0 ml of saline over 2 minutes. VIP was infused using a Harvard 22 pump, infusing at 500μl/min via a 3-way tap into the femoral vein. After VIP infusion, the catheter was flushed with heparinised saline (Hepsaline) so that no VIP was left in the catheter.

For experiments using VIP infusions, there was a need for an initial sensitising single dose of 60μg/kg, in order that reproducible responses could be obtained. An initial infusion of Hepsaline (50UI/ml) was infused to act as a negative control.

(f) Infusion of test compound to achieve 0.03nM to 10nM free plasma concentration

To achieve steady state plasma concentrations of the test compound, a loading dose was administered followed by infusion of a steady state dose. The test compound was made up in saline and details of the infusion protocols are given in the Table below. Test compound and vehicle controls were infused at the same rate. The test compound was infused for 15 minutes prior to pelvic nerve stimulation.

Infusion number	Target Plasma Concentration (nM free)	Loading Infusion (μg/kg/min i.v.) 10 minutes	Maintenance Infusion (μg/kg/min i.v.) 10 minutes
1	0.03	0.04	0.003
2	0.1	0.08	0.01
3	0.3	0.24	0.03
4	1.0	0.84	0.1
5	3.0	2.4	0.3
6	10.0	8.4	1.0

(g) Statistical Analysis

All data are reported as mean ± s.e.m. (Standard error of the mean). Significant changes were identified using Student's t-tests (independent).

Vehicle treated VIP-induced increases in vaginal blood flow were compared with UK-447,841 (21 x IC_{50}) treated VIP-induced increases in vaginal blood flow using paired Student's t-test.

Example 2: Binding assay to α_1 receptor subtypes

Binding assays to the α_1 receptor subtypes can be carried out by standard techniques, well known to the skilled person. In brief, transfected cells expressing human or mammalian α_1 adrenergic receptor subtypes (Schwinn, D.A. (1995) J. Pharmacol. Exp. Ther. 272, 134-142; Schwinn, D.A. et al (1990) J. Biol. Chem. 265, 8183-8189; Cotecchia, S. et al (1988) Proc. Natl. Acad. Sci. USA 85, 7159-7163; Lomasney, J.W. et al (1991) J. Biol. Chem. 266, 6365-6369) are scraped into 50mM Tris-HCl, pH7.5, and lysed by sonication. The cell lysates are centrifuged at 1000rpm for 5 min at 4°C. The supernatant is centrifuged at 30,000xg for 20 min at 4°C. The pellet is resuspended in 50mM Tris-HCl. Binding of the α_1 antagonist [^{3}H]-prazosin (0.3nM final concentration) is carried out at room temperature for 30 minutes. Non-specific binding is determined in the presence of 10μM phentolamine. The reaction is stopped by filtration through GF/B filters presoaked in 50mM Tris/HCl, 0.5% polyethylenimine PEI (w/v), and the radioactivity on the filters measured by scintillation counting. Inhibition experiments are caried out with a range of concentration of test compound; the results are analysed using non-linear regression curve fitting computer programs for obtain K_i values.

Example 3: Functional assays - contractile responses in various tissues

(a) Contractile responses of rabbit aorta (α_{1L} receptor)

A single rabbit aorta was cleaned of connective tissue, cut into rings ~3mm in length, then denuded of epithelium by rubbing very gently with a probe. The lengths of tissue are then mounted in the 5ml organ baths, which contain the modified Krebs of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The tissues are placed under ~1.5g tension, and are left to equilibrate for ~60 minutes on a pump speed of ~5ml\minute, adjusting the tension to 1-1.5g if necessary after 15 and 45 minutes. A 1M stock solution ($1x10^{-3}$M bath conc) of methoxamine in water was made and 1:10 dilutions made using the same diluent. A sensitising dose of 120mM KCl (bath concentration) was added to each bath. After the maximum response had been reached (usually about 6-8 minutes), the tissues are washed with Krebs for 60 minutes, pump speed at ~2.97ml/min.

A cumulative dose response curve was constructed, bath concentrations of methoxamine being $1x10^{-7}$M to a maximum of $3x10^{-4}$M. Each dose was allowed to exert its maximum effect before the next dose was added (6-8 mins). On completion of this curve, the tissues were washed, (pump speed ~10ml/min for 10 minutes, 2.97ml/min for 50 minutes) until the tissues were stable at baseline tension.

The compound under investigation was made up to a stock concentration of 1mM in 100% DMSO. Three chosen concentrations for a pA_2 estimation were then made up in DMSO, and 5µl of each concentration added in duplicate to the tissues, with a vehicle control (DMSO). The tissues were left in the presence of compound or vehicle for 60 minutes before a second CDRC to methoxamine was constructed up to a maximum of $3x10^{-3}$M

The data was captured on ADA analysis in-vitro software, which expresses the readings as a % of the maximum response of the control curve, draws control and test compound dose response curves, and calculates a EC_{50} and then dose ratio (DR), the ratio between control and treatment curve EC_{50}, for each treatment. The results are reported as pK_b, or where possible pA_2.

$$pKb = \frac{-\log [\text{Antagonist concentration}]}{(DR^* - 1)}$$

where $DR^* = \frac{\text{dose ratio compound}}{\text{dose ratio control}}$

NB. If the value of (DR*-1) was less than or equal to 2, the result could not be used for a pA_2 estimation. The control curves must not have shifted by more than 2.5. The pA_2 was plotted on a Schild analysis. ie y axis = log (DR*-1); x axis = - log antagonist concentration

(b) Contractile responses of rat vas deferens (α_{1A} receptor)

Rat vas deferens were cleaned of associated blood vessels and connective tissue, and the epidydimal (thinner) end cut to ~15mm in length. The lengths of tissue were mounted in 5ml organ baths, which contain the modified Krebs of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The tissues were placed under to ~1g tension,

and left to equilibrate for ~60 minutes on a pump speed of ~5ml\minute. The tension is adjusted during this period to ~ 1g to stabilise the resting tension. A 0.1M stock solution of noradrenaline (NA) was made in dilute ascorbic acid solution (0.1mg/ml), and 1:10 dilutions made using the same diluent. A sensitising dose of $1x10^{-4}$M noradrenaline, was added to each bath. After the maximum response had been reached (~ 1 minute), the tissues were washed with Krebs for 1 hour, pump speed at ~2.97ml/min. A control non-cumulative dose response curve (NCDRC) is constructed, using 0.5 log dose increments, bath concentrations of NA being : $1x10^{-8}$M to $3x10^{-5}$M. Following each response the tissues were washed at 5ml/min for 5 minutes prior to the next concentration being added. All reading were for 90 seconds reading the "area under the curve" for each response. On completion of this curve, the tissues were washed (pump speed max for 5 seconds, 2.97ml/min for 60 minutes).

The compound under investigation is made up to a stock concentration of 1mM in 100% DMSO. Three chosen concentrations for a pA_2 estimation were then made up in 1litre of the modified Krebs, and perfused over tissues in duplicate, with a Krebs + vehicle (DMSO) for control, for 60 minutes, pump speed 2.97ml/min. A second NCDRC to NA was constructed ($1x10^{-8}$ to $3x10^{-3}$M) in all tissues as described above, using the relevant antagonist-Krebs solution for washes between responses.

The data was captured on ADA analysis in-vitro software, which expresses the readings as a % of the maximum response of the control curve, draws control and test compound dose response curves, and calculates a EC_{50} and then dose ratio (DR), the ratio between control and treatment curve EC_{50}, for each treatment. The results are reported as pK_b, or where possible pA_2.

$$pKb = \frac{-\log [\text{Antagonist concentration}]}{(DR^* - 1)}$$

where $DR^* = \frac{\text{dose ratio compound}}{\text{dose ratio control}}$

NB. If the value of (DR*-1) was less than or equal to 2, the result could not be used for a pA_2 estimation. The control curves must not have shifted by more than 2.5. The pA_2 was plotted on a Schild analysis. ie y axis = log (DR*-1); x axis = - log antagonist concentration

(c) Contractile responses of rat aorta (α_{1D} receptor)

Rat aortae were cleaned of connective tissue, cut to ~3mm in length, then denuded of epithelium by rubbing very gently with a probe. The lengths of tissue are then mounted in the 5ml organ baths, which contain the modified Krebs of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The tissues were placed under ~1g tension, and were left to equilibrate for ~60 minutes on a pump speed of ~5ml\minute, adjusting the tension to 1-1.5g if necessary after 15 and 45 minutes. A 0.1M stock solution of noradrenaline (NA) was made in dilute ascorbic acid solution (0.1mg/ml), and 1:10 dilutions made using the same diluent. A sensitising dose of $1x10^{-6}$M noradrenaline (bath concentration) was added to each bath. After the maximum response had been reached (usually about 3-4 minutes), the tissues were washed with Krebs for 30 minutes, pump speed at ~2.97ml/min.

A cumulative dose response curve was constructed, bath concentrations of NA being $1x10^{-9}$M to a maximum of $1x10^{-6}$M. Each dose was allowed to exert its maximum effect before the next dose was added (2-4mins). On completion of this curve, the tissues were washed, (pump speed ~10ml/min for 10 minutes, 2.97ml/min for 20 minutes) until the tissues were stable at baseline tension.

The compound under investigation was made up to a stock concentration of 1mM in 100% DMSO. Three chosen concentrations for a pA_2 estimation were made up in DMSO, and 5µl of each concentration added in duplicate to the tissues, with a vehicle control (DMSO). The tissues were left in the presence of compound or vehicle for 60 minutes.

A second CDRC to NA was constructed as described previously, up to a maximum of $3x10^{-3}$M

The data was captured on ADA analysis in-vitro software, which expresses the readings as a % of the maximum response of the control curve, draws control and test compound dose response curves, and calculates a EC_{50} and then dose ratio (DR), the ratio between control and treatment curve EC_{50}, for each treatment. The results are reported as pK_b, or where possible pA_2.

$$pKb = \frac{-\log [\text{Antagonist concentration}]}{(DR^* - 1)}$$

where DR* = dose ratio compound
dose ratio control

NB. If the value of (DR*-1) was less than or equal to 2, the result could not be used for a pA_2 estimation. The control curves must not have shifted by more than 2.5. The pA_2 was plotted on a Schild analysis. ie y axis = log (DR*-1); x axis = - log antagonist concentration

(d) Contractile responses of rat spleen (α_{1B} receptor)

Rat spleens were cleaned of connective tissue, the ends removed and cut longitudinally in two. The lengths of tissue were then mounted in the 5ml organ baths, which contain modified Krebs of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The tissues were placed under 1g tension, and were left to equilibrate for ~90 minutes on a pump speed of ~3ml\minute. Tissue tension was not adjusted during this period. Tissue tension equilibrated to ~500-700mg. A 0.1M stock solution of noradrenaline (NA) was made in dilute ascorbic acid solution (0.1mg/ml), and 1:10 dilutions made using the same diluent. A sensitising dose of $1x10^{-4}$M noradrenaline, was added to each bath. After the maximum response had been reached (~ 6 minutes), the tissues were washed with Krebs for 90minutes, pump speed ~3ml/min. A second sensitising dose of $1x10^{-4}$M noradrenaline was then added as above and upon reaching the maximum response, the tissues were washed with Krebs as above. A cumulative dose response curve (CDRC) was constructed, bath concentrations of phenylephrine being : $1x10^{-8}$M to $3x10^{-4}$M.

The compound under investigation was made up to a stock concentration of 1mM in 100% DMSO. Three chosen concentrations for a pA_2 estimation were made up in DMSO, and 5µl of each concentration added in duplicate to the tissues, with a vehicle control (DMSO). The tissues were left in the presence of compound or vehicle for 60 minutes. A second CDRC to NA was constructed as described previously, up to a maximum of $3x10^{-3}$M

The data was captured on ADA analysis in-vitro software, which expresses the readings as a % of the maximum response of the control curve, draws control and test compound

dose response curves, and calculates a EC_{50} and then dose ratio (DR), the ratio between control and treatment curve EC_{50}, for each treatment. The results are reported as pK_b, or where possible pA_2.

$$pKb = \frac{-\log [\text{Antagonist concentration}]}{(DR^* - 1)}$$

where $DR^* = \frac{\text{dose ratio compound}}{\text{dose ratio control}}$

NB. If the value of (DR*-1) was less than or equal to 2, the result could not be used for a pA_2 estimation. The control curves must not have shifted by more than 2.5. The pA_2 was plotted on a Schild analysis. ie y axis = log (DR*-1); x axis = - log antagonist concentration

(e) Contractile responses of human prostate (α_{1L} receptor)

Prostatic tissue was cut into longitudinal strips (approximately 3x2x10 mm) and suspended in organ baths under a resting tension of 1 g in Krebs Ringer bicarbonate of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The solution also contained 10 mM cocaine and 10 mM corticosterone. Tissues were sensitised using a full concentration-response curve to (-)-noradrenaline (100nM to 30μM) and then washed over a 60 minute period. Isometric contractions were obtained in response to cumulative additions of (-)-noradrenaline to obtain control curves in all tissues. A further curve was then generated in the presence or absence of antagonist (incubated for 2 hours). Antagonist affinity estimates (pA_2) were determined using a single concentration of competing antagonist, $pA_2 = -\log [A]/(DR-1)$ where the dose ratio (DR), relative to corresponding controls, was produced by a single concentration of antagonist [A], assuming competitive antagonism and Schild regression close to unity.

Claims:

1. Use of a compound which is an α_{1A} and/or an α_{1L} antagonist, in the manufacture of a medicament for the treatment of FSD.

2. Use as claimed in claim 1, wherein the IC_{50} of the compound in a functional assay as an α_{1A} and/or an α_{1L} antagonist is less than 100nM.

3. Use as claimed in claim 1 or claim 2, wherein the potency of the compound as an α_{1A} and/or an α_{1L} antagonist is less than 10 nM.

4. Use as claimed in any one of claims 1 to 3, wherein the potency of the compound as an α_{1A} and/or an α_{1L} antagonist is less than 1 nM.

5. Use as claimed in any one of claims 1 to 4, wherein the compound is a selective α_{1L} antagonist and/or a selective α_{1A} antagonist.

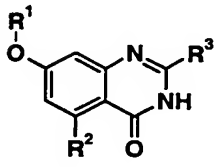
6. Use as claimed in claim 5, wherein the compound is more than 10 fold selective for α_{1L} and/or α_{1A} over α_{1B}.

7. Use as claimed in claim 5, wherein the compound is more than 10 fold selective for α_{1L} and/or α_{1A} over α_{1D}.

8. Use as claimed in any one of claims 5, 6, or 7, wherein the compound is more than 10 fold selective for α_{1L} and/or α_{1A} over α_{1D} and α_{1B}.

9. Use as claimed in any previous claim, wherein FSD is FSAD and/or FOD.

10. Use as claimed in claim 1, wherein the compound is a compound of formula (I):



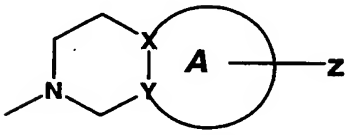
(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents C_{1-4} alkyl;

R^2 represents C_{3-6} cycloalkyl;

R^3 represents a bicyclic group of the formula



wherein X and Y are selected from C and N, provided that at least one is C;

Ring A together with X and Y represents a 5- or 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms in the ring;

Z is selected from H, and LR^4;

L represents a direct link, C_{1-4} alkylene or C_{1-4} alkoxyalkylene;

R^4 represents H, NR^5R^6, C_{3-6} cycloalkyl, OR^7 or Het^1;

R^5 and R^6 are independently selected from H, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with OR^8;

R^7 is selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{3-6}cycloalkyl, Het^2 and C_{1-4}alkyl-Het^3;

R^8 is H or C_{1-4} alkyl;

Het^1, Het^2 and Het^3 independently represent a 4 to 7 membered saturated heterocyclic group which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, O or S, optionally substituted with OR^9 and/or C_{1-4} alkyl optionally substituted by OR^9;

R^9 is H or C_{1-4} alkyl.

11. Use as claimed in claim 10, wherein the compound is selected from the following compounds:

5-cyclopropyl-7-methoxy-2-(2-([dimethylamino]methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(1-pyrrolidinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-([dimethylamino]methyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-pyrrolidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-piperidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(4-morpholinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro[1,6]naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone, or pharmaceutically acceptable salts or solvates thereof.

12. Use as claimed in claim 5, wherein the compound is 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable salt or solvent thereof.

13. A method of treating FSD comprising the administration to a patient in need of such treatment of an effective amount of an α_{1A} and/or an α_{1L} antagonist.

14. An intravaginal formulation comprising a compound as defined in any preceding claim.

15. A formulation as claimed in claim 14, which is a creme or a gel.

16. A method of enhancing sexual function in a female comprising administering an α_{1A} and/or an α_{1L} antagonist to a healthy female.

17. A method of screening for compounds useful for treating FSD, comprising screening compounds for antagonist activity against α_{1A} and/or α_{1L} adrenergic receptor and selecting compounds with an IC_{50} of less than 100nM.

APPENDIX 1

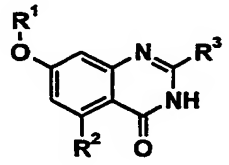
Compounds Useful in Therapy

This invention relates to novel compounds useful in therapy. It also relates to compositions containing such derivatives and to their use. They have potential utility in the treatment of hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia.

International Patent Application WO 97/23462 discloses quinoline and quinazoline compounds having a 5-phenyl substituent. The compounds are indicated in the treatment of benign prostatic hyperplasia.

International Patent application WO 98/30560 discloses quinoline and quinazoline compounds indicated in the treatment of benign prostatic hyperplasia.

According to the present invention, there are provided compounds of the formula (I):



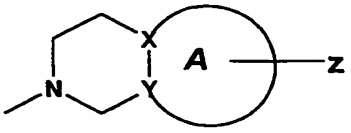
(I)

and pharmaceutically acceptable salts or solvates thereof, wherein

R^1 represents C_{1-4} alkyl;

R^2 represents C_{3-6} cycloalkyl;

R^3 represents a bicyclic group of the formula



wherein X and Y are selected from C and N, provided that at least one is C;

Ring A together with X and Y represents a 5- or 6-membered aromatic ring containing 0, 1, 2 or 3 nitrog n atoms in the ring;

Z is selected from H, and LR^4;

L represents a direct link, C_{1-4} alkylene or C_{1-4} alkoxyalkylene;

R^4 represents H, NR^5R^6, C_{3-6} cycloalkyl, OR^7 or Het^1;

R^5 and R^6 are independently selected from H, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with OR^8;

R^7 is selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{3-6}cycloalkyl, Het^2 and C_{1-4}alkyl-Het^3;

R^8 is H or C_{1-4} alkyl;

Het^1, Het^2 and Het^3 independently represent a 4 to 7 membered saturated heterocyclic group which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, O or S, optionally substituted with OR^9 and/or C_{1-4} alkyl optionally substituted by OR^9;

R^9 is H or C_{1-4} alkyl.

In the above definitions alkyl, alkoxy and cycloalkyl groups containing the requisite number of carbon atoms, except where indicated, can be unbranched- or branched-chain. Examples of alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Unless oth rwise provided herein:

WSCDI means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

DCC means N,N'-dicyclohexylcarbodiimide;

HOAT means 1-hydroxy-7-azabenzotriazole;

HOBT means 1-hydroxybenzotriazole hydrate;

PyBOP® means Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate;

PyBrOP® means bromo-tris-pyrrolidino-phosphonium hexafluorophosphate;

Mukaiyama's reagent means 2-chloro-1-methylpyridinium iodide;

KHMDS means potassium bis(trimethylsilyl)amide;

Hünig's base means N-ethyldiisopropylamine;

Et_3N means triethylamine;

NMM means N-methylmorpholine;

DEAD means diethyl azodicarboxylate;

DIAD means diisopropyl azodicarboxylate;

DIBAL-H means diisobutylaluminium hydride;

BINAP means 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;

Dba means dibenzylideneacetone;

Boc means *tert*-butoxycarbonyl;

CBz means benzyloxycarbonyl;

$(Boc)_2O$ means di-*tert*-butyl dicarbonate;

MeOH means methanol, EtOH means ethanol, and EtOAc means ethyl acetate;

THF means tetrahydrofuran, DMSO means dimethyl sulphoxide, and DCM means dichloromethane;

AcOH means acetic acid, TFA means trifluoroacetic acid.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen

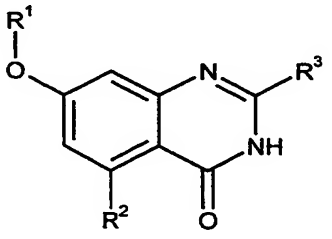
phosphate, acetate, maleate, fumerate, lactat , tartrate, citrate, gluconate, succinat , saccharate, benzoate, methan sulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and palmoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts. For a review on suitable salts see Berge et al, J. Pharm. Sci, 66, 1-19, 1977.

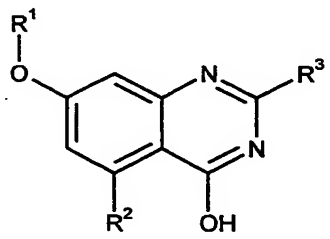
The pharmaceutically acceptable solvates of the compounds of the formula (I) or salts thereof include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

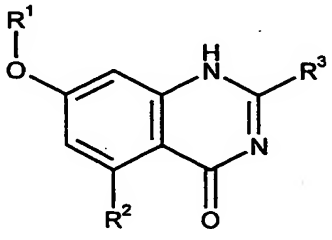
A compound of the formula (I) may contain one or more asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of formula (I) along with the individual tautomeric forms (1a, 1b and 1c) thereof, together with mixtures thereof.



1a



1b



1c

Separation of diastereoisomers may be achiev d by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared

from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

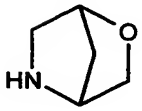
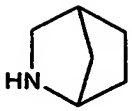
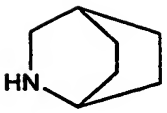
The present invention also includes all suitable isotopic variations of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. An isotopic variation of a compound of the formula (I) or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the formula (I) and pharmaceutically acceptable salts there of include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the compounds of the formula (I) and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for exampl , increased *in vivo* half-life or reduced dosage requirements and hence may b preferred in some circumstances. Isotopic variations of the compounds of formula (I) and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

Preferred groups of compounds that may be mentioned include those in which:

Het^{1}, Het^{2} and Het^{3} contain at least one N atom and are linked through an N atom.

More preferred groups of compounds include those in which:

Het^{1}, Het^{2} and Het^{3} include azetidine, pyrrolidine, piperidine, piperazine, azepane, morpholine, homomorpholine, or one of the following ring systems


optionally substituted by OR^9, C_{1-4} alkyl optionally substituted by OR^9.

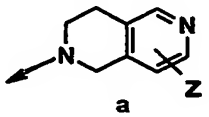
Still more preferred groups of compounds that may be mentioned include those in which:

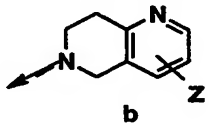
(a) R^1 is CH_3;

(b) R^2 is cyclopropyl;

(c) L is methylene;

(d) R^3 represents a group chosen from a or b (bonded to the quinazolinone through the N-atom as indicated)

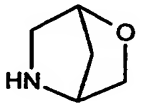

a


b

where Z is CH_2Het^1 or $CH_2NR^5R^6$;

(e) R^5 and R^6 are independently selected from H or C_{1-3} alkyl optionally substituted by OCH_3;

(f) Het^1, Het^2 and Het^3 are selected from the group comprising pyrrolidine, piperidine, morpholine or



Compounds that may be prepared according to the invention, amongst others, are:

5-cyclopropyl-7-methoxy-2-(2-([dimethylamino]methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(1-pyrrolidinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-([dimethylamino]methyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-pyrrolidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-piperidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(4-morpholinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro[1,6]naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone;

and pharmaceutically acceptable salts or solvates thereof.

The compounds of the invention are useful because they possess pharmacological activity in animals. In particular, the compounds are useful in the treatment of a number of conditions including hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia. The latter condition is of greatest interest.

Thus, according to another aspect of the invention, there is provided a pharmaceutical composition including a compound of the formula (I), a tautomer, or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier. Also provided is a method of treatment of benign prostatic hyperplasia which comprises administering a therapeutically effective amount of a compound of the invention to a patient suffering from such a disorder. The use of the compounds of the invention as pharmaceuticals, and the use of the compounds of the invention in the manufacture of a medicament for the treatment of benign prostatic hyperplasia, are also provided.

The compounds of the invention may be administered by any convenient route, for example orally, parenterally (*e.g.* intravenously, transdermally) or rectally. The daily

dose required will of course vary with the particular compound used, the particular condition being treated and with the sev rity of that condition. However, in general a total daily dose of from about 0.01 to 10.0 mg/kg of body weight, and preferably about 0.01 to 2.5 mg/kg, is suitable, administered from 1 to 2 times a day. Oral administration is of particular interest.

The compounds of the invention will generally be administered in the form of a suitable pharmaceutical formulation. Thus, according to another aspect of the invention, there is provided a pharmaceutical formulation including preferably less than 50% by weight of a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical formulation is preferably in unit dose form. Such forms include solid dosage forms, for example tablets, pills, capsules, powders, granules, and suppositories for oral, parenteral or rectal administration; and liquid dosage forms, for example sterile parenteral solutions or suspensions, suitably flavoured syrups, flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, and elixirs and similar pharmaceutical vehicles. Oral formulations are preferably controlled-release formulations.

Solid formulations may be prepared by mixing the active ingredient with pharmaceutical carriers, for example conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and other diluents, for example water, to form a homogeneous preformulation formulation in which the active ingredient is uniformly dispersed so that it may be readily subdivided into equally effective unit dosage forms containing typically from 1.0 to about 70.0 mg of the active ingredient. The solid dosage forms may be coated or otherwise compounded to prolong the action of the formulation.

Formulations may contain a compound of the invention in combination with a compound that attenuates the growth of the prostate gland. For example, a formulation is envisaged that combines a compound of the invention with human

5-α reductase inhibitory compound [see International Patent Application WO 95/28397]. Alternatively, a compound of the invention could be presented in a pharmaceutical pack also containing a human 5-α reductase inhibitory compound as a combined preparation for simultaneous, separate or sequential use.

The compounds of the invention may be tested in th screen set out below:

Contractil responses of rabbit aorta (α_{1L} rec ptor)

A single rabbit aorta was cleaned of connective tissue, cut into rings ~3mm in length, then denuded of epithelium by rubbing very gently with a probe. The lengths of tissue are then mounted in the 5mL organ baths, which contain the modified Krebs of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The tissues are placed under ~1.5g tension, and are left to equilibrate for ~60 minutes on a pump speed of ~5mL\minute, adjusting the tension to 1-1.5g if necessary after 15 and 45 minutes. A 1M stock solution ($1x10^{-3}$M bath conc.) of methoxamine in water was made and 1:10 dilutions made using the same diluent. A sensitising dose of 120mM KCl (bath concentration) was added to each bath. After the maximum response had been reached (usually about 6-8 minutes), the tissues are washed with Krebs for 60 minutes, pump speed at ~2.97mL/min.

A cumulative dose response curve was constructed, bath concentrations of methoxamine being $1x10^{-7}$M to a maximum of $3x10^{-4}$M. Each dose was allowed to exert its maximum effect before the next dose was added (6-8 mins). On completion of this curve, the tissues were washed, (pump speed ~10mL/min for 10 minutes, 2.97mL/min for 50 minutes) until the tissues were stable at baseline tension.

The compound under investigation was made up to a stock concentration of 1mM in 100% DMSO. Three chosen concentrations for a pA_2 estimation were then made up in DMSO, and 5µl of each concentration added in duplicate to the tissues, with a vehicle control (DMSO). The tissues were left in the presence of compound or vehicle for 60 minutes before a second CDRC to methoxamine was constructed up to a maximum of $3x10^{-3}$M

The data was captured on ADA analysis in-vitro software, which expresses the readings as a % of the maximum response of the control curve, draws control and test compound dose response curves, and calculates a EC_{50} and then dose ratio (DR), the ratio between control and treatment curve EC_{50}, for each treatment. The results are reported as pK_b, or where possible pA_2.

$$pKb = -\log \frac{[\text{Antagonist concentration}]}{(DR^* - 1)}$$

where $DR^* = \frac{\text{dose ratio compound}}{\text{dose ratio control}}$

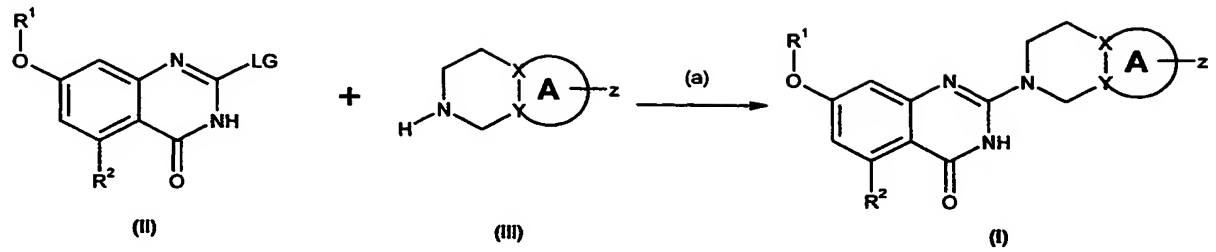
NB. If the value of (DR*-1) was less than or equal to 2, the result could not be used for a pA_2 estimation. The control curves must not have shifted by more than 2.5. The pA_2 was plotted on a Schild analysis. i.e. y axis = log (DR*-1); x axis = -log antagonist concentration

The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stabl , have fewer side effects or are more selective (in particular they may have beneficial effects in benign prostatic hyperplasia without causing undesirable cardiovascular effects, for example because they are able to selectively antagonise prostatic receptor subtypes of the α_1-adrenoceptor), or have other more useful properties than the compounds of the prior art.

All of the compounds illustrated in examples 1 to 46 display pA2 values versus α1L (in the above method) of greater than 7.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional techniques, for example as described in `Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

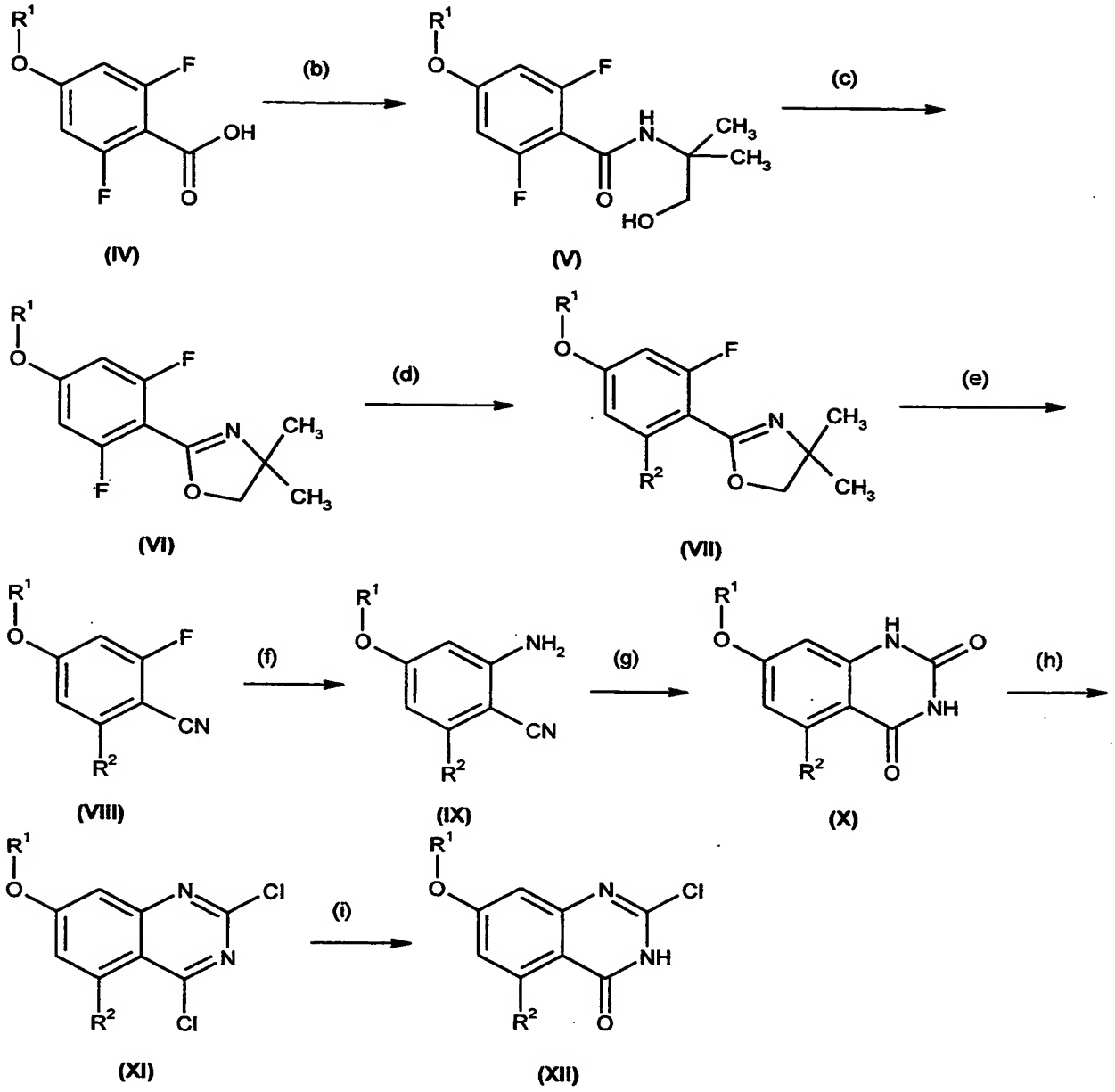
The compounds of the invention may be obtained by the reaction of an amine (III) with alkylating agent (II) as shown in the sch me below, where R^1, R^2, R^3 etc. are as previously defined:



Scheme 1.

Step (a): Amine (III) is reacted with quinazolinone (II), where LG is a suitabl leaving group (for example halo, tosylate or mesylate), in the presence of an excess of 3° amine base (as H^+ acceptor) (for example Et_3N, Hünig's base or NMM) in a suitable high boiling solvent at elevated temperature for 1-6 hrs. For example, preferred conditions for a) are 1-2 eq amine (III), 1.5-8 eq of 3° amine base (for example Et_3N or Hünig's base), in n-BuOH at reflux for 1-6 hours. Preferably leaving group LG is Halo. More preferably LG is Cl.

Quinazolinone (II) may be prepared according to scheme 2, where R^1 and R^2 are as previously defined:



Scheme 2.

Step (b): This acid/amine coupling may be undertaken by using either

(i) an acyl chloride derivative of acid (IV) + amine, with an excess of acid acceptor in a suitable solvent, or

(ii) the acid (IV) with a conventional coupling agent + amine, optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent.

Typically the conditions are as follows:

(i) acid chloride of acid (IV) (generated in-situ), an excess of amine, optionally with an excess of 3° amine such as Et_3N, Hünig's base or NMM, in DCM or THF, without heating for 1 to 24 hrs,

or

(ii) acid (IV), WSCDI /DCC and HOBT /HOAT, an excess of amine, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 48 hrs; or, acid (IV), PYBOP®/PyBrOP®/Mukaiyama's reagent, an excess of amine, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 24 hrs.

The preferred conditions are: acid chloride of acid (IV) (generated in-situ), 3.6 eq amine, in DCM at rt. for 1hrs.

Step (c): The hydroxy group of compound (V) is converted into a suitable leaving group (LG, where LG is halo, mesylate, or tosylate), followed by an in-situ alkylation/ring formation.

Typically LG is halo. It is preferred that LG is Cl. Chlorination is carried out under standard conditions, using a chlorinating agent ($SOCl_2$, $POCl_3$) optionally in the presence of a 3° amine base (e.g. Hünig's base, Et_3N), optionally in a suitabl solvent (DCM) at room temperature to reflux temperature for 1-16 hours. Preferred conditions are: 1.1 eq $SOCl_2$, in DCM for 1.5 hrs at rt.

Step (d): An organometallic addition/elimination is undertaken by reacting fluoro compound (VI) with "activated" R^2 (such as R^2MgBr, R^2MgCl, R^2Li), in a suitable solvent (tetrahydrofuran, ether, cyclohexane, 1,4-dioxane) at 0°C to room temperature for 1-24 hrs. Preferred conditions are: 1-2 eq. of R^2MgBr or R^2MgCl (generated in-situ, using standard Grignard methodology), 1 eq of fluoro compound (VI), in tetrahydrofuran, at between 0°C and room temperature, for 3 hours.

Step ( ): The nitril (VIII) is preferably formed from compound (VII) under the following conditions: 2 eq $POCl_3$, 10 eq pyridine, EtOAc, reflux for 5 hours.

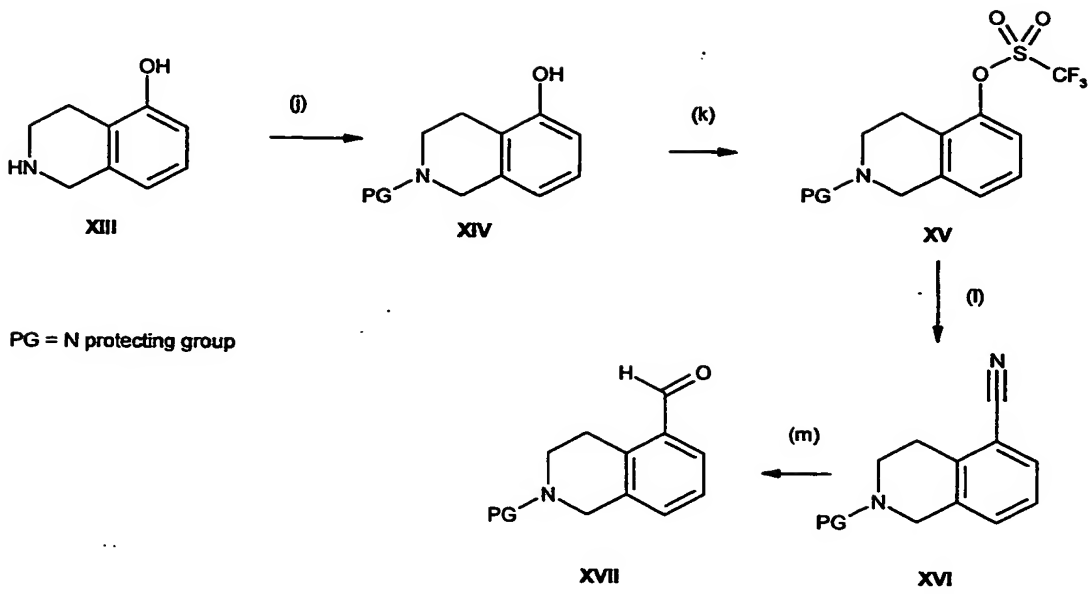
Step (f): Amination of compound (VIII) is achieved by reaction with R^aNH_2 (R^a is H) at an elevated temperature and pressure, in a suitable solvent (DMSO, MeOH) for about 18-72 hrs. It is preferred to carry out the reaction under the following conditions: R^aNH_2 in DMSO at elevated temperature (about 140°C) and pressure (sealed vessel) for 18-72 hrs.

Step (g): Quinazolinedione (X) is formed by CO_2 insertion, derived from the method of Mizuno et. al. Tet. Lett. 41 (2000) 1051. The following conditions are preferred: 2 eq of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), CO_2 (solid), in N,N-dimethylformamide, at 140°C and elevated pressure (sealed vessel) for 18 hrs.

Step (h): This chlorination step can be done under standard conditions, using an excess of chlorinating agent ($SOCl_2$, $POCl_3$) optionally in the presence of a 3° amine base (e.g. Hünig's base, Et_3N), optionally in a suitable solvent (DCM) at room temperature to reflux temperature for 1-16 hours. It is preferred to use the following conditions: 30 eq $POCl_3$ (as solvent), optionally in the presence of a base, e.g. 2.4 eq Hünig's base, at reflux for 1-7 hours

Step (i): Selective hydrolysis of compound (XI) is achieved by reaction with an OH^- source (typically an alkali metal hydroxide) in a suitable solvent, at room temperature for 2 hours. Preferred conditions are: 3 eq NaOH(aq) in dioxane at room temperature for 2 hours.

Suitable amines for use as compound (III) may be prepared as described below in schemes 3 to 13:

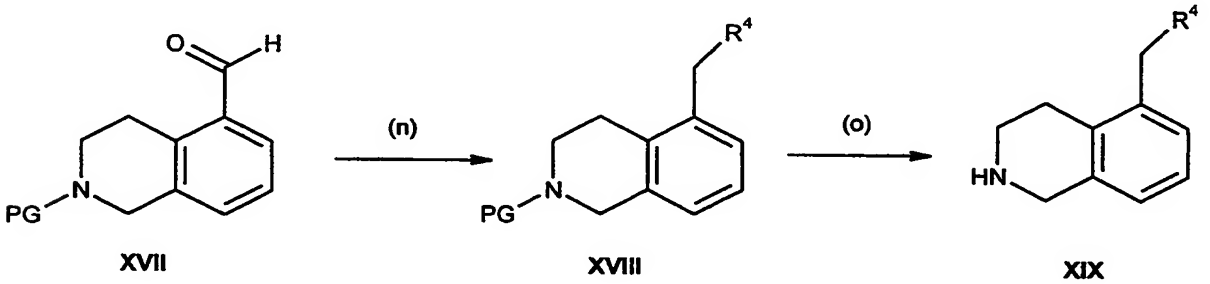


PG = N protecting group

Scheme 3.

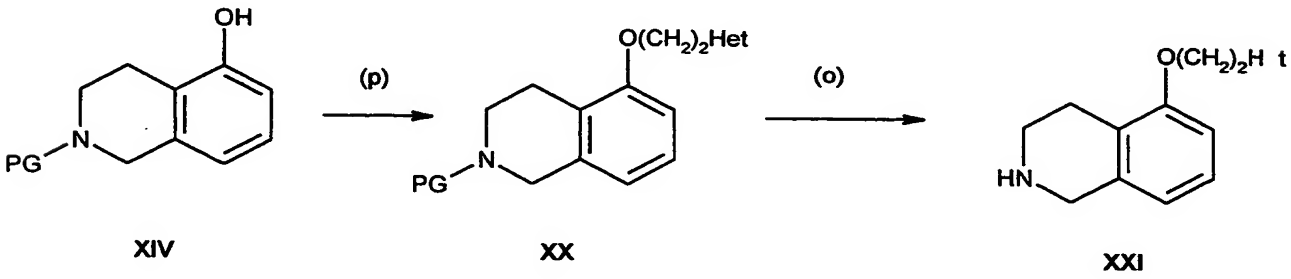
Compounds XVII and XIV can then be further elaborated according to schemes 4 and 5 respectively:

When R^4 represents NR^5R^6 or an N-linked Het,



PG= N protecting group

Scheme 4.



PG = N protecting group

Sch m 5.

Step (j): The amine (XIII) is protected using standard methodology for introducing nitrogen protecting groups, such as that found in textbooks, (e.g. "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz). It is preferred to use the *tert*-butoxycarbonyl (Boc) protecting group which is introduced under the following conditions: 2.3 eq $(Boc)_2O$, in dioxane/1N NaOH solution (1:2 by volume) at room temperature for 16 hrs.

Step (k): Triflate (XV) is formed by reaction of alcohol (XIV) with a slight excess of a suitable triflating reagent, in the presence of an excess of a 3° amine base (e.g. Et_3N, NMM, Hünig's base) in a suitable solvent (DCM) at between 0°C and room temperature for up to 24 hours. Preferred conditions are as follows: 1.1 eq N-phenylbis(trifluoromethanesulphonimide), 1.1 eq Et_3N, in DCM at 0°C and room temperature for 16 hours.

Step (l): Nitrile (XVI) is obtained via metal catalysed (preferably palladium, nickel) cross-coupling with a suitable nitrile source (e.g. $Zn(CN)_2$), in the presence of a suitable additive (preferably LiCl) in a suitable solvent at elevated temperature for up to 24 hrs. It is preferred to use the following conditions: 1 eq $Zn(CN)_2$, 1 eq LiCl, cat $Pd(PPh_3)_4$, in N,N-dimethylformamide at 110°C for 8 hrs.

Step (m): Nitrile (XVI) is reduced with a suitable metal hydride reducing agent ($LiAlH_4$, $NaAlH_4$, DIBAL-H) in a suitable solvent (toluene, tetrahydrofuran) at low temp (-78°C), followed by acid or base catalysed hydrolysis of the intermediate imine compound to give aldehyde (XVII). Preferred conditions are: 2 eq DIBAL-H, in toluene at -78°C for 2 hrs, then MeOH, HCl at -78°C to 0°C.

Step (n): Aldehyde (XVII) is reacted with an amine (NR^5R^6 or N-linked Het) to form an intermediate compound, which is reduced by a suitable reducing agent, such as $NaCN(BH)_3$ or $Na(OAc)_3BH$, optionally in the presence of NaOAc or AcOH, optionally in the presence of a drying agent (molecular sieves, $MgSO_4$) in a suitable solvent (tetrahydrofuran, DCM) at room temperature for 3-72 hrs. Preferred conditions are: 1-2 eq amine, 2-5 eq of $Na(OAc)_3BH$, optionally with 1-4

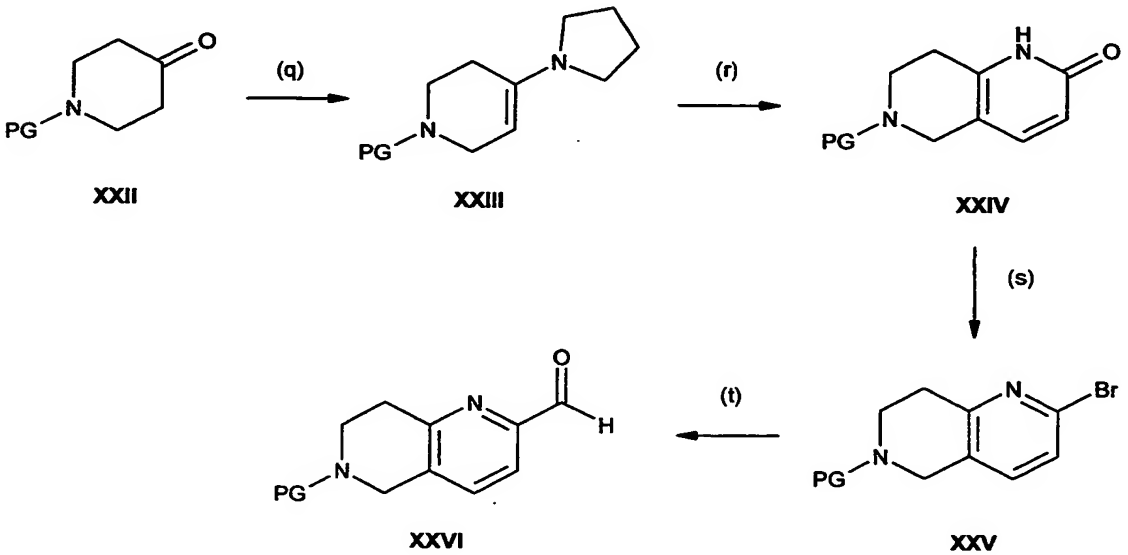
eq of AcOH or NaOAc, optionally in the presence of 3Å sieves, in tetrahydrofuran at room temperature for 3-72 hrs.

Step (o): Deprotection is undertaken using standard methodology, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz".

When PG is Boc, then preferred conditions are: HCl(g) in DCM or MeOH at rt. for 30 min to 2 hrs, or DCM:TFA (1:1 by volume) at room temperature for 3 hrs.

When PG is benzyl, then the preferred conditions are: 10% Pd/C (1:1 w/w), 2-25 eq ammonium formate or formic acid, in MeOH at reflux for between 3 mins and 1.5 hrs, or 10% Pd/C (about 10% w/w), in methanol, optionally in the presence of HCl, at about 30°C and 30psi for about 17 hrs.

Step (p): A Mitsunobu reaction between alcohol (XIV) and $HO(CH_2)_2Het$ is carried out using standard methodology, as discussed in Synthesis 1 (1981) or Org. React. 42; 335 (1992). Preferred conditions are: 2.1 eq DEAD (Diethylazodicarboxylate), 2.25 eq PPh_3, 2.65 eq of $HO(CH_2)_2Het$, in DCM for 34 hrs at rt.



Schem 6.

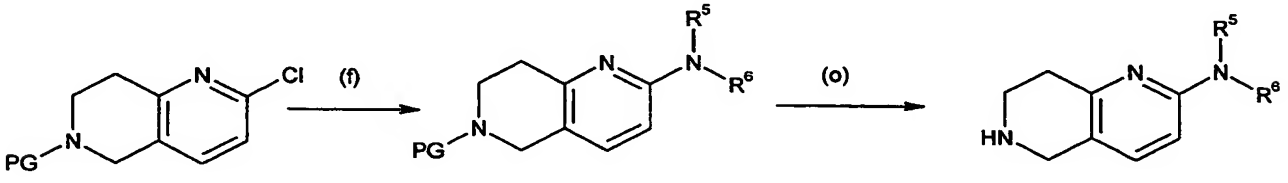
Step (q): Compound (XXII) is reacted with an amine, with the concomittant removal of water, in a suitable high boiling solvent, at an elevated temperature for up to 48 hours, to give compound (XXIII). The following conditions are preferred: 1.5 eq pyrrolidine and ketone (XXII) in toluene at reflux under Dean and Stark conditions, for 4.5 hrs.

Step (r): 2 equivalents of propiolamide to 1 equivalent of compound (XXIII) in a high boiling solvent (e.g. Toluene) at reflux for 16 hours.

Step (s): Compound (XXIV) is brominated using standard methodology, with a suitable brominating agent ($POBr_3$), optionally in the presence of anisole, in a suitable solvent (MeCN), at elevated temp for about 1 hr. The following conditions are preferred: 5 eq of $POBr_3$, in MeCN/anisole (1:1 by volume) at 120°C for 1 hr.

Step (t): Metalation of compound (XXV) is undertaken with a suitable base (nBuLi) at low temp (-78°C), followed by quench of the intermediate anion by an excess of formyl source (N,N-dimethylformamide) for about 1 hr, to give compound (XXVI). Preferred conditions are: 1.1-1.5 eq n-BuLi, tetrahydrofuran, -78°C, for 5-15min, then 3eq N,N-dimethylformamide for 1 hour.

Compound (XXVI) can then be further elaborated by reductive amination followed by deprotection in a manner similar to that depicted in scheme 4.
Compounds (XXVII) and (XXV) can be further elaborated according to schemes 7 and 8 respectively:

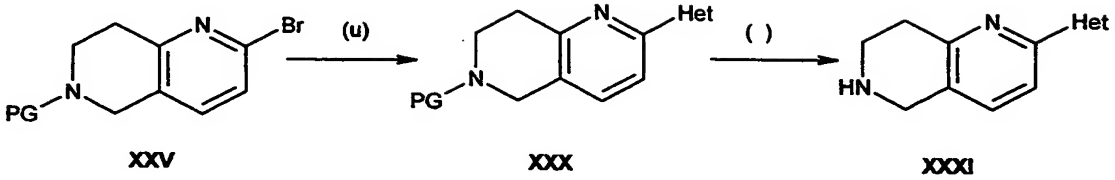


XXVII XXVIII XXIX

[for the transformation of compound XXVII to XXVIII the general conditions outlined in (f) apply however amine R^5R^6NH is used]

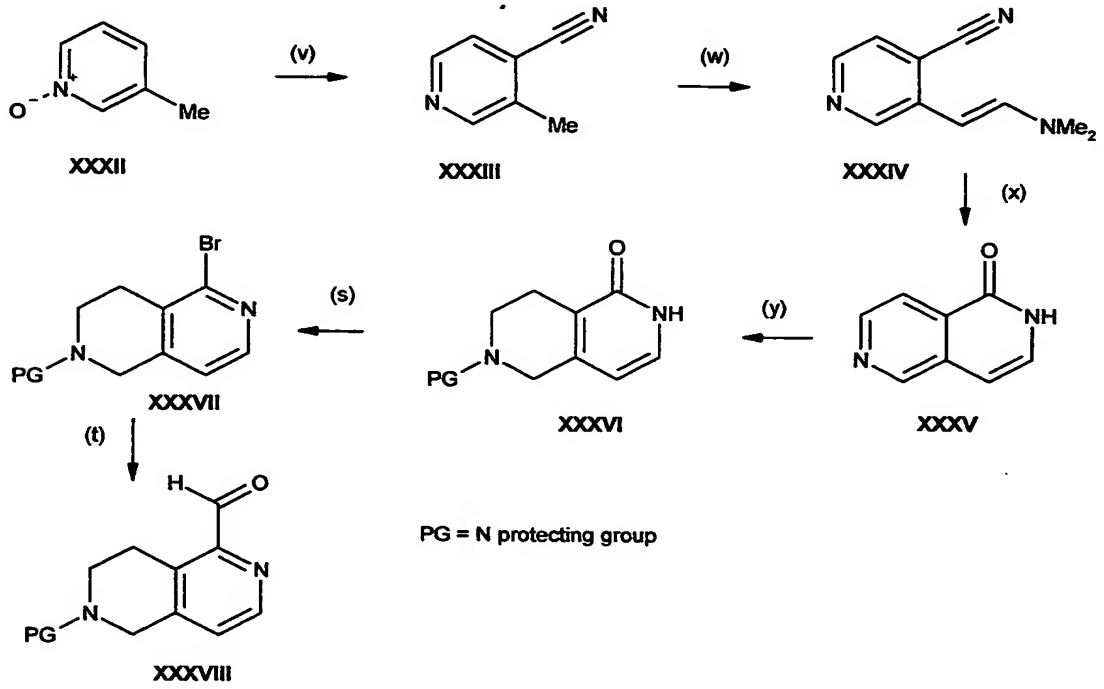
Scheme 7.

When Het is linked through N,



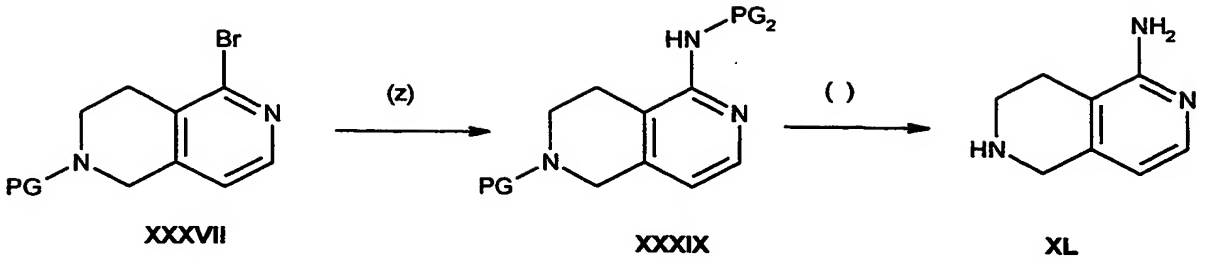
Scheme 8.

Step (u): A palladium catalysed cross-coupling reaction is undertaken using a suitable base (Na*t*-BuO), a catalytic amount of suitable additive and suitable palladium catalyst in toluene at elevated temp for 18 hrs, to give compound (XXX). The preferred conditions are: 1.5 eq N-linked Het, (e.g. morpholine), 1.5 eq Na*t*-BuO, 0.08eq BINAP, 0.04 eq $Pd(dba)_3$, in toluene at 100°C for 18 hrs.



Scheme 9.

Compound (XXXVIII) may be further elaborated in a manner analogous to that shown in scheme 4.



PG and PG2 = N protecting groups

Scheme 10.

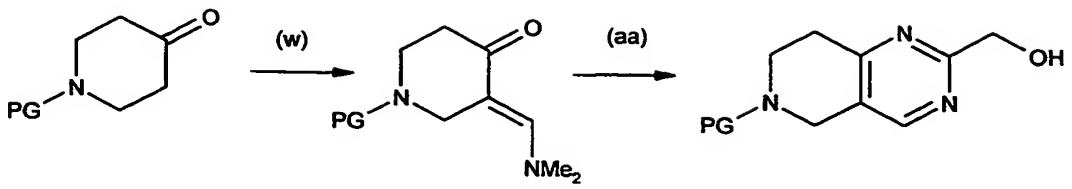
Step (v): O-alkylation and addition by cyanide is undertaken using the preferred conditions of 3 eq EtI, in DCM at rt. for 16 hrs, followed by 2 eq NaCN in H_2O at 60°C for 1 hr.

Step (w): Condensation with N,N-dimethylformamide dimethylacetal is undertaken using the preferred conditions: Substrate (XXXIII) in N,N-dimethylformamide/N,N-dimethylformamide dimethylacetal (1:1 to 1:10 by volume) as solvent, at reflux for 8-16 hrs.

Step (x): Cyclisation is undertaken using the preferred conditions: substrate (XXXIV) in EtOH/48% HBr (about 1:1 by volume) for 18 hour.

Step (y): Protection of the N atom of (XXXV) followed by reduction is achieved using standard methodology, e.g. PG is Benzyl, followed by reduction of the ring using a suitable reducing agent (e.g. $NaBH_4$). Preferred conditions are 1.5eq benzyl bromide, in MeCN at reflux for 2 hours, followed by an excess of $NaBH_4$ in EtOH at 0°C to rt. for 16 hrs.

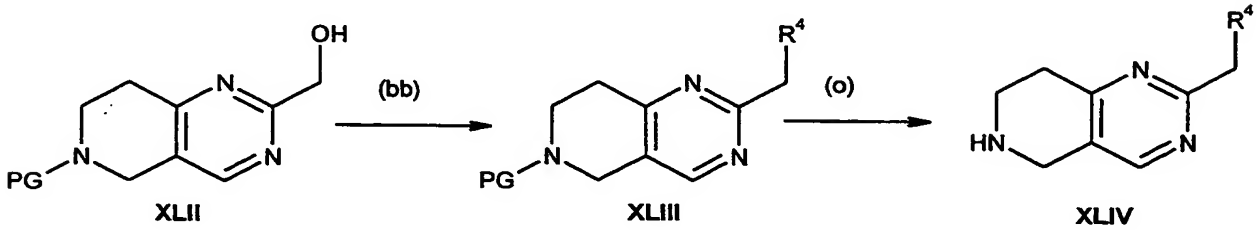
Step (z): Excess amine ($NHPG_2$) is reacted with the bromide (XXXVII), optionally in the presence of a 3° amine base, at elevated temperature for up to 24 hrs leading to formation of compound (XXXIX). Preferably an excess of amine $NHPG_2$ (as solvent) is used, at 160°C for 12 hrs.



XXII XLI XLII

Scheme 11.

Compound (XLII) can then be elaborated according to scheme 12 below, when R^4 represents NR^5R^6 or an N-linked Het:



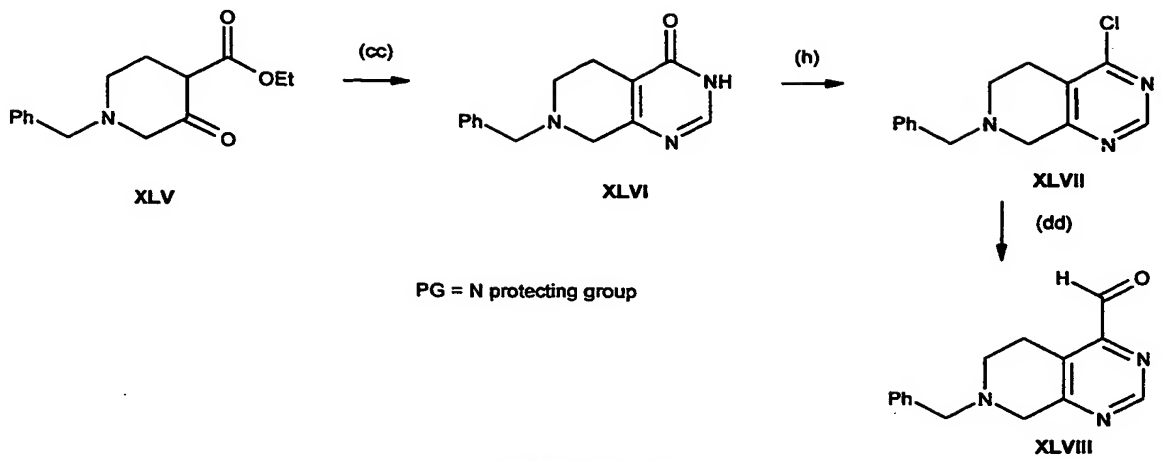
XLII XLIII XLIV

PG = N protecting group

Scheme 12.

Step (aa): Condensation of compound (XLI) is achieved with a suitabl formamidine in the presence of a suitable base (alkali metal alkoxide, or hydride, such as NaOEt, NaH) in a suitable solvent (e.g. EtOH) at elevated temperature. Preferred conditions are: NaOEt, (generated in-situ), carbonyl compound (XLI), slight excess of ($NH_2CH(N)CH_2OH$), in EtOH at reflux for 3 hours.

Step (bb): Alcohol (XLII) is reacted, in-situ, to form a suitable alkylating agent (halo, mesylate, tosylate), followed by reaction with an excess of NR^5R^6 or an N-linked Het, in the presence of a 3° amine base (Et_3N, Hünig's base) in a suitable solvent. The preferred conditions are: 1.2 eq MsCl, 2.5 eq-5 eq NR^5R^6 or an N-linked Het,, 1.5-2.2 eq. base (Et_3N, Hünig's base) in DCM or tetrahydrofuran for 1-18 hrs between rt. and reflux.

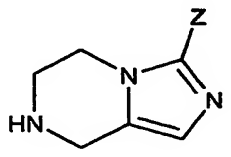


Scheme 13.

Compounds XLVIII may then be elaborated further in an analogous manner to scheme 4.

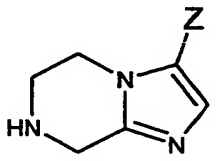
Step (cc): Condensation of the compound (XLV) is undertaken with a suitable formamidine in the presence of a suitable base (alkali metal alkoxide, or hydride, such as NaOEt, NaH) in a suitable solvent (e.g. alcohol, EtOH) at elevated temperature. The preferred conditions are: 2.3 eq NaOEt (generated in-situ), dicarbonyl compound (XLV), 1.1eq formamidine acetate in EtOH at reflux for 40 hrs.

Step (dd)-Metalation of compound (XLVII) is undertaken following the method of Kondo et. al (J. Chem. Soc., Perkin Trans. 1, 1996), followed by quench of the intermediate anion by an excess of formyl source (eg N,N-dimethylformamide), to provide compound (XLVIII). Preferred conditions are: 1.1eq Te, 1.12 eq n-BuLi, tetrahydrofuran at rt for 30 mins, then 1.12eq n-BuLi, excess N,N-dimethylformamide at -78°C for 45 mins.



XLIX

Compounds of formula (XLIX) may be prepared by analogy to the methods described in JP 07101959, and to those described herein, from readily available starting materials using appropriate reagents and reaction conditions.



L

Compounds of formula (L) may be prepared by analogy to the method described in WO 97/30053, and to those described herein, from appropriate aminomethylketones, prepared in accordance with the method of Yinglin and Hongwen, Synthesis 1990; 615, and other readily available starting materials.

It will be appreciated by one skilled in the art that further elaboration of suitable R^4 groups (for example those containing a "reactive" N atom) may be achieved using standard chemical transformations (for example alkylation, reductive amination) as previously described herein. Furthermore, it will be appreciated that standard protecting and deprotecting group strategies may be employed.

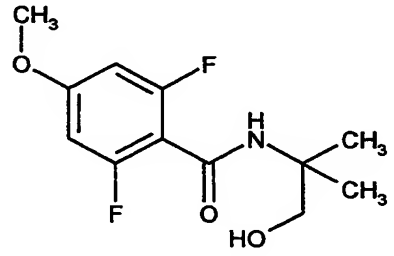
The following preparations describe the preparation of certain intermediate compounds used for the synthesis of compounds of the formula (I):

Spectroscopic data were recorded on a Finnigan Mat. Navigator (LRMS, eith r positive (ES^+) or negative (ES^-) electrospray mode), and Varian Unity Inova-400 (NMR, 400 MHz) instruments and are consistent with the assigned structures. Optical rotations were obtained using a Perkin Elmer 341 polarimeter.
Combustion analyses were performed by Exeter Analytical (UK) Limited, Uxbridge, Middlesex. Reactions were performed under an atmosphere of dry nitrogen unless otherwise noted. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualised using UV light, 5% aqueous potassium permanganate or chloroplatinic acid/potassium iodide solution.

In cases where compounds were analysed as hydrates, the presence of water was evident in the enhanced peak due to water in the NMR spectra. The purity of compounds was carefully assessed using analytical TLC and proton NMR (400 MHz), and the latter was used to calculate the amount of solvent in solvated samples. In multistep sequences, the purity and structure of intermediates were verified spectroscopically by NMR and LRMS.

Preparation 1

2,6-Difluoro-*N*-(2-hydroxy-1,1-dimethylethyl)-4-methoxybenzamide



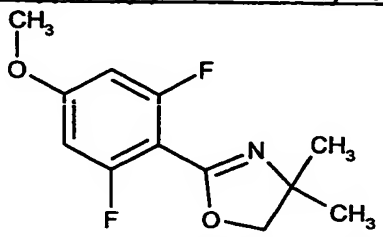
The 2,6-difluoro-4-methoxybenzoic acid (Mol. Cryst. Liq. Cryst. 1989; 172; 165) (2.09g, 11.1mmol) was suspended in dichloromethane (110mL) and a few drops of N,N-dimethylformamide was added followed by oxalyl chloride (2.79g, 22.2mmol). The reaction mixture was stirred for 45 minutes at room temperature, after which time a clear homogeneous solution had formed. The reaction mixture was concentrated under reduced pressure and redissolved in dichloromethane (100mL). The reaction mixture was then added slowly to an ice-cold solution of amino-2-methylpropanol (3.56g, 40mmol), in dichloromethane (50mL). After stirring at room temperature for 1 hour, the reaction mixture was washed with water (75mL), 0.2N hydrochloric acid (50mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound as a white solid (2.77g, 96%).

^{1}H-nmr ($CDCl_3$, 1.38 (s, 6H), 3.70 (m, 2H), 3.80 (s, 3H), 5.90 (bs, 1H), 6.42 (2xs, 2H).

LRMS : m/z (ES^+) 260 [MH^+]

Preparation 2

2-(2,6-Difluoro-4-m thoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole



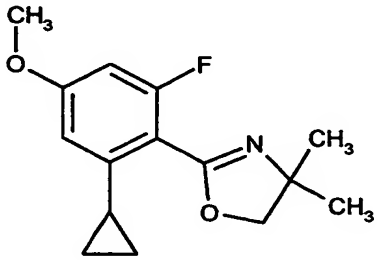
To a solution of the alcohol from preparation 1 (2.75g, 10.6mmol) in anhydrous dichloromethane (50mL) was added thionyl chloride (1.43g, 12mmol) and the reaction stirred for 1.5 hours at room temperature. The reaction mixture was poured into 1M sodium hydroxide solution (50mL) and extracted with dichloromethane (2 x 50mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with dichloromethane:methanol 96:4) to give the title compound as a clear oil (2.40g, 94%).

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.40 (s, 6H), 3.80 (s, 3H), 4.04 (s, 2H), 6.42 (m, 2H).

LRMS : m/z (ES^+) 242 [MH^+]

Preparation 3

2-(2-Cyclopropyl-6-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole



To a solution of cyclopropyl bromide (12.1g, 100mmol) in anhydrous tetrahydrofuran (100mL) was added magnesium turnings (2.4g, 100mmol) followed by a crystal of iodine, at room temperature. After a few minutes the reaction initiated and came to reflux without any additional heating. When the reflux was complete the reaction was cooled to room temperature and stirred for 2 hours. A solution of the fluoro compound from preparation 2 (9.64g, 40mmol) in tetrahydrofuran (50mL) was cooled in an ice-bath to 0°C, and the grignard solution

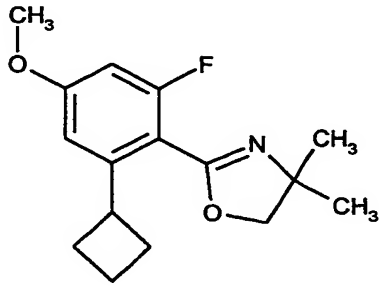
(50mL) was added dropwise over 15 minutes, the cooling bath was removed and reaction warmed to room temperature and stirred for 1 hour. Further grignard solution (20mL) was added and stirred for 1 hour. Further grignard solution (10mL) was added and stirred for 1 hour. The reaction mixture was then quenched with 1M citric acid (30mL), as some solid remained undissolved 2M hydrochloric acid (30mL) was added. The resultant mixture was partitioned between ethyl acetate (400mL) and water (200mL), basified with concentrated ammonia solution and the organic layer separated, washed with water (150mL), brine (150mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with hexane:isopropyl alcohol 85:15) to give the title compound as a clear oil (10.32g, 98%).

^{1}H-nmr ($CDCl_3$, 40MHz) δ: 0.66 (m, 2H), 0.94 (m, 2H), 1.40 (s, 6H), 2.18 (m, 1H), 3.78 (s, 3H), 4.07 (s, 2H), 6.25 (s, 1H), 6.42 (m, 1H).

LRMS : m/z (ES^+) 286 [MNa^+]

Preparation 4

2-(2-Cyclobutyl-6-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole



To a solution of cyclobutyl chloride (5.64g, 62mmol) in anhydrous tetrahydrofuran (60mL) was added magnesium turnings (1.56g, 65mmol) followed by a crystal of iodine, at room temperature. The mixture was stirred at room temperature for 1 hour, followed by a further hour under reflux. A solution of the fluoro compound from preparation 2 (7.23g, 30mmol) in tetrahydrofuran (80mL) was cooled in an ice-bath to 0°C, and the grignard solution (40mL) was added dropwise over 15 minutes, the cooling bath was removed and reaction warmed to room temperature and stirred for 2 hours. Further grignard solution (10mL) was added and the

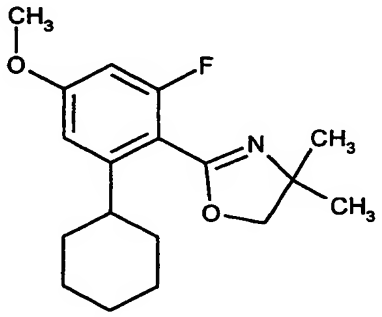
reaction stirred for a further 30 minutes. The reaction was poured into a solution of ethylenediaminetetraacetic acid disodium salt (12g) in 1N sodium hydroxide (100mL), and the mixture extracted with ethyl acetate (1x200mL, 2x100mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure, to afford the title compound as a pale yellow oil, 8.31g.

^{1}H-nmr ($CDCl_3$, 40MHz) δ: 1.43 (s, 6H), 1.77-1.88 (m, 1H), 1.91-2.07 (m, 1H), 2.07-2.20 (m, 2H), 2.24-2.36 (m, 2H), 3.82 (s, 3H), 3.83 (m, 1H), 4.10 (s, 2H), 6.48 (dd, 1H), 6.66 (d, 1H).

LRMS : m/z (APCI$^+$) 278 [MNH_4^+]

Preparation 5

2-(2-Cyclohexyl-6-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole



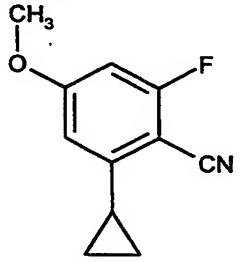
Cyclohexylmagnesium chloride (22mL, 2M in diethyl ether, 44mmol) was added slowly to an ice-cooled solution of the compound from preparation 2 (9.64g, 40mmol) in tetrahydrofuran (100mL), and the solution then stirred at room temperature for 2 hours. Water (10mL) was added, the mixture poured into ethyl acetate, and washed with a solution of ethylenediaminetetracetic acid disodium salt (24g) in water (200mL), then 1N sodium hydroxide solution (100mL) and brine. The organic solution was dried ($MgSO_4$) and evaporated under reduc d pressure to afford the title compound as a colourless oil, 12.4g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.15-1.50 (m, 10H), 1.76 (d, 2H), 1.84 (m, 2H), 1.90 (m, 2H), 2.86 (m, 1H), 3.80 (s, 3H), 4.13 (s, 2H), 6.47 (dd, 1H), 6.63 (d, 1H).

LRMS : m/z (APCI$^+$) 306 [MH^+]

Preparation 6

2-Cyclopropyl-6-fluoro-4-methoxybenzonitrile



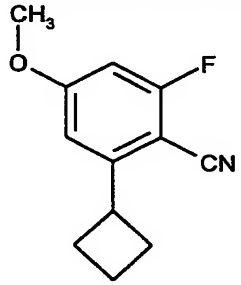
Pyridine (31.6g, 400mmol) was added to a solution of the compound from preparation 3 (10.32g, 39.2mmol) in ethyl acetate (150mL), followed by phosphorous oxychloride (12.27g, 80mmol). The reaction was stirred at reflux for 5 hours, cooled and poured onto ice. This aqueous mixture was extracted with ethyl acetate, the organic solution washed with 2M hydrochloric acid, and brine then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane to afford the title compound as a white solid, 6.41g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.88 (m, 2H), 1.16 (m, 2H), 2.20 (m, 1H), 3.80 (s, 6H), 6.21 (s, 1H), 6.49 (m, 1H).

LRMS : m/z (ES^+) 214 [MNa^+]

Preparation 7

2-Cyclobutyl-6-fluoro-4-methoxybenzonitrile



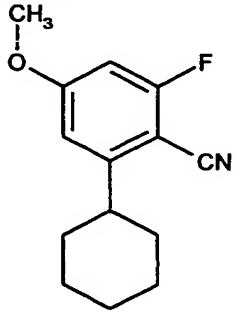
The title compound was obtained as a pale yellow oil in 99% yield from the compound from preparation 4, following a similar procedure to that described in preparation 6, except the compound was isolated without column chromatography.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.78-1.94 (m, 1H), 1.99-2.24 (m, 3H), 2.41-2.55 (m, 2H), 3.81 (m, 1H), 3.87 (s, 3H), 6.53 (dd, 1H), 6.69 (d, 1H).

LRMS : m/z (APCI$^+$) 223 [MNH_4^+]

Preparation 8

2-Cyclohexyl-6-fluoro-4-methoxybenzonitril



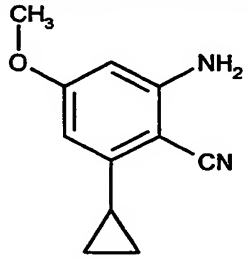
The title compound was obtained as a colourless oil in 93% yield from the compound from preparation 5, following a similar procedure to that described in preparation 6.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.18-1.57 (m, 4H), 1.73-1.96 (m, 6H), 2.85-2.96 (m, 1H), 3.85 (s, 3H), 6.54 (dd, 1H), 6.65 (d, 1H).

LRMS : m/z (APCI$^+$) 251 [MNH_4^+]

Preparation 9

2-Amino-6-cyclopropyl-4-methoxybenzonitrile

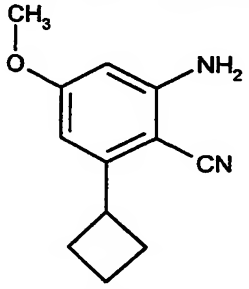


The fluoro compound from preparation 6 (3.0g, 15.7mmol) was added to a saturated solution of 0.88 ammonia in dimethylsulphoxide (20mL), and the solution stirred in a sealed vessel for 18 hours at 150°C. The cooled mixture was partitioned between ethyl acetate and water and the layers separated. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane as eluant to afford the title compound as a white crystallin solid, 1.28g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.74 (m, 2H), 1.02 (m, 2H), 2.10 (m, 1H), 3.76 (s, 6H), 4.38 (bs, 2H), 5.82 (s, 1H), 6.00 (s, 1H).
LRMS : m/z (ES^+) 211 [MNa^+]

Preparation 10

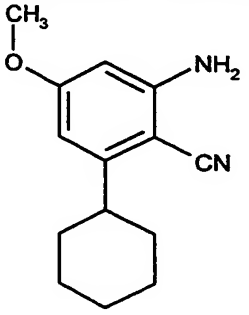
2-Amino-6-cyclobutyl-4-methoxybenzonitrile



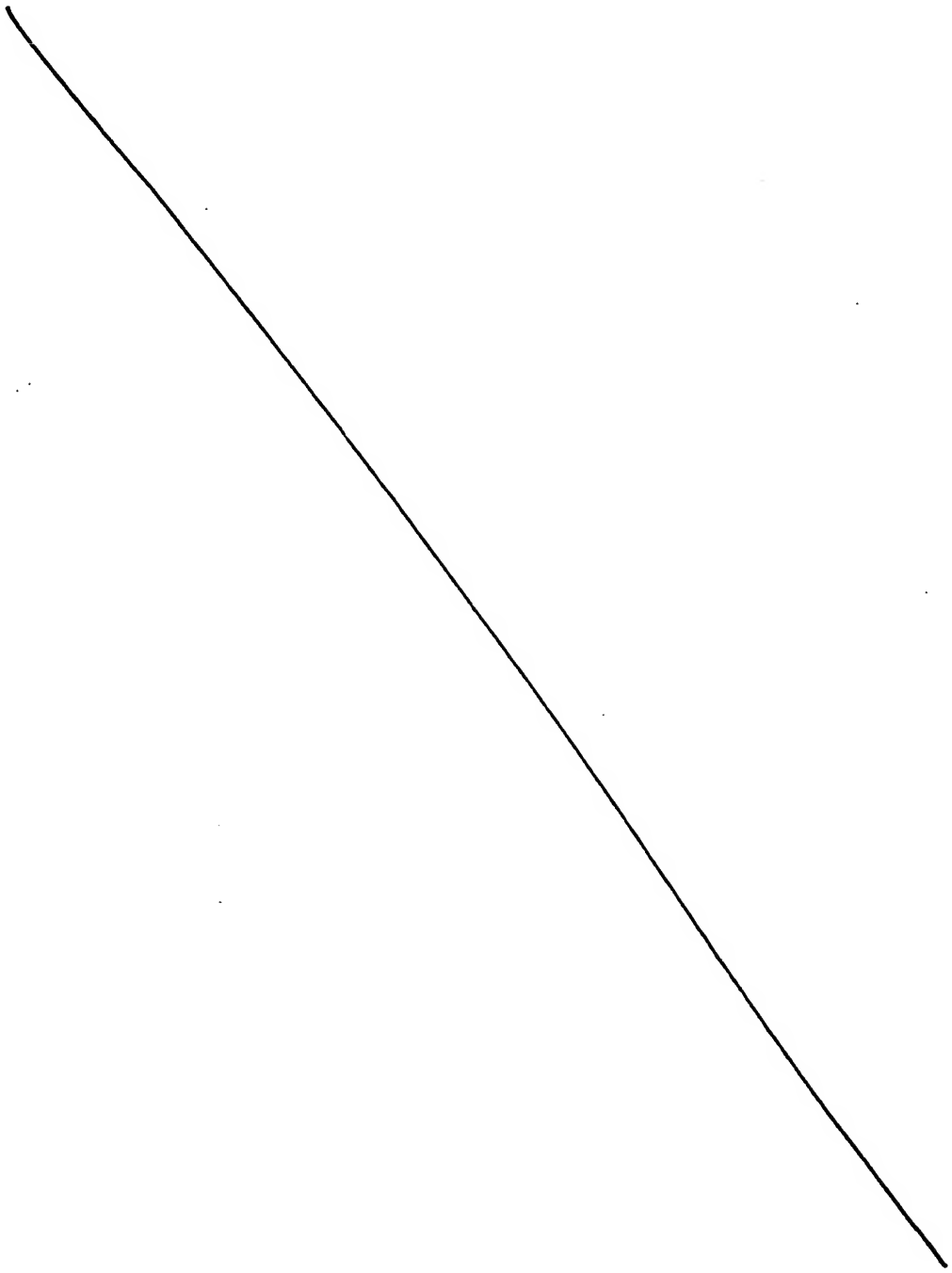
The title compound was obtained as a white solid in 54% yield from the fluoro compound from preparation 7, following a similar procedure to that described in preparation 9, except dichloromethane:ethyl acetate (100:0 to 80:20) was used as the column eluant.
^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.76-1.90 (m, 1H), 1.94-2.21 (m, 3H), 2.37-2.49 (m, 2H), 3.66-3.77 (m, 1H), 3.80 (s, 3H), 4.06-4.43 (bs, 2H), 6.05 (s, 1H), 6.27 (s, 1H).
LRMS : m/z (ES^+) 225 [MNa^+]

Preparation 11

2-Amino-6-cyclohexyl-4-methoxybenzonitrile

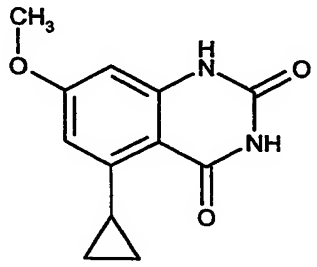


The title compound was obtained as a yellow solid in 44% yield from the fluoro compound from preparation 8, following the procedure described in preparation 9.
^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.17-1.53 (m, 5H), 1.72-1.96 (m, 5H), 2.80 (m, 1H), 3.78 (s, 3H), 6.05 (d, 1H), 6.22 (d, 1H).
LRMS : m/z ($APCI^+$) 231 [MH^+]



Preparation 12

5-Cyclopropyl-7-methoxy-2,4(1*H*,3*H*)-quinazolinedione



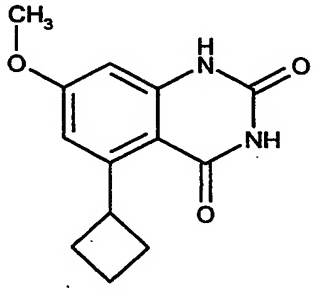
A solution of the compound from preparation 9 (1.25g, 6.65mmol) in N,N-dimethylformamide (10mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2mL) was cooled to -78°C, and solid carbon dioxide added. The reaction vessel was sealed and heated to 140°C for 18 hours. The cooled mixture was poured into wat r (150mL), then acidified using 2N hydrochloric acid, and the mixture stirred for 10 minutes. The resulting precipitate was filtered off, washed with water and acetone, to afford the title compound as a white solid, 1.44g.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 0.68 (m, 2H), 0.95 (m, 2H), 3.40 (m, 1H), 3.76 (s, 3H), 6.18 (s, 1H), 6.42 (s, 1H).

LRMS : m/z (ES$^-$) 231 [M-H$^-$]

Preparation 13

5-Cyclobutyl-7-methoxy-2,4(1*H*,3*H*)-quinazolinedione



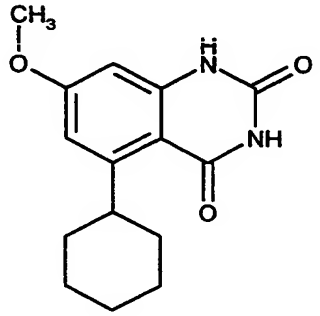
The title compound was obtained as an off-white solid in 75% yield, from the compound from preparation 10, following the procedure described in preparation 12.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.72 (m, 1H), 1.81-2.05 (m, 3H), 2.29 (m, 2H), 3.81 (s, 3H), 4.45 (m, 1H), 6.50 (d, 1H), 6.62 (d, 1H), 10.79 (s, 1H), 10.85 (s, 1H).

LRMS : m/z (APCI$^-$) 245 [M-H$^-$]

Preparation 14

5-Cyclohexyl-7-m thoxy-2,4(1*H*,3*H*)-quinazolin dione



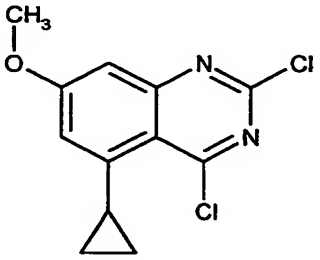
The title compound was obtained as a white solid in 77% yield, from th compound from preparation 11, following the procedure described in preparation 12.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.14-1.45 (m, 5H), 1.63-1.82 (m, 5H), 3.78 (s, 3H), 4.08 (t, 1H), 6.50 (d, 1H), 6.58 (d, 1H), 10.80 (s, 1H), 10.85 (s, 1H).

LRMS : m/z (APCI$^-$) 273 [M-H$^-$]

Preparation 15

2,4-Dichloro-5-cyclopropyl-7-quinazolinyl methyl ether



To a solution of the compound from preparation 12 (3.87g, 16.7mmol) in phosphorous oxychloride (50mL) was added N,N-diisopropylethylamine (5.17g, 40mmol). The reaction mixture was heated at 100°C for 1 hour, at reflux for 6 hours then cooled to room temperature. The phosphorous oxychloride was removed under reduced pressure. The resultant oil was partitioned between ethyl acetate (500mL) and ice-water (300mL), the layers were separated, the organic phase washed with 1M hydrochloric acid (100mL), brine (100mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column

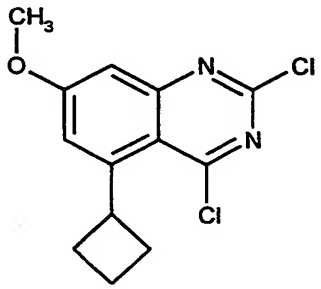
chromatography on silica gel eluting with a solvent gradient of dichloromethane:ethyl acetate (100:0 to 94:6) to give the title compound as a white solid (3.97g, 88%).

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.84 (m, 2H), 1.17 (m, 2H), 2.70 (m, 1H), 2.94 (s, 3H), 7.10 (s, 1H), 7.14 (s, 1H).

LRMS : m/z (ES^+) 291 [MNa^+]

Preparation 16

2,4-Dichloro-5-cyclobutyl-7-quinazolinyl methyl ether



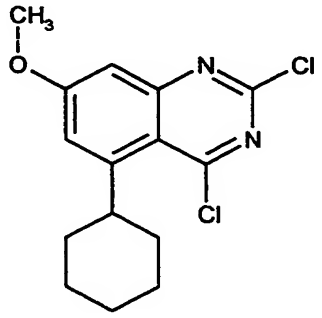
To a solution of the compound from preparation 13 (2.46g, 10mmol) in phosphorous oxychloride (25mL) was added N,N-diisopropylethylamine (3.1g, 24mmol) and the reaction mixture was heated at reflux for 7 hours then cooled to room temperature. The solution was poured cautiously onto ice, diluted with water, and the mixture extracted with dichloromethane (3x100mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:ethyl acetate (100:0 to 94:6) to give the title compound as a white solid, 1.74g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.84-1.94 (m, 1H), 2.00-2.23 (m, 3H), 2.49-2.60 (m, 2H), 3.97 (s, 3H), 4.60 (m, 1H), 7.14 (d, 1H), 7.27 (d, 1H).

LRMS : m/z (ES^+) 305 [MNa^+]

Preparation 17

2,4-Dichloro-5-cycloh xyl-7-quinazolinyl methyl eth r



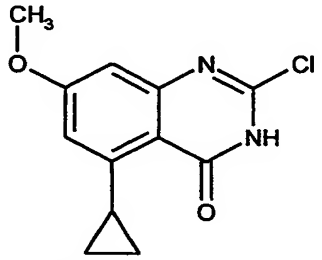
The title compound was obtained as a white solid in 64% yield, from the compound from preparation 14, following the procedure described in preparation 16.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.21-1.60 (m, 5H), 1.73-2.07 (m, 5H), 3.96 (s, 3H), 4.05 (m, 1H), 7.16 (d, 1H), 7.23 (d, 1H).

LRMS : m/z ($APCI^+$) 311 [MH^+]

Preparation 18

2-Chloro-5-cyclopropyl-7-methoxy-4(3*H*)-quinazolinone



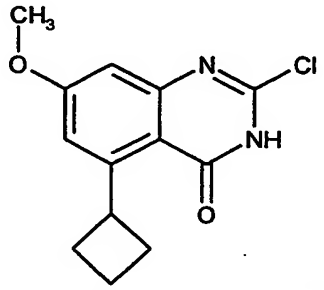
1N Sodium hydroxide solution (30mL) was added to a solution of the chloro compound from preparation 15 (2.2g, 8.18mmol) in dioxane (50mL) and the reaction stirred at room temperature for 2 hours. The reaction was acidified using 2M hydrochloric acid and extracted with dichloromethane:methanol (95:5) (3x150mL). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound as a white solid, 1.85g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.73 (m, 2H), 1.09 (m, 2H), 3.31 (m, 1H), 3.86 (s, 3H), 6.60 (d, 1H), 6.89 (d, 1H).

LRMS : m/z (ES^+) 273 [MNa^+]

Preparation 19

2-Chloro-5-cyclobutyl-7-methoxy-4(3*H*)-quinazolinone



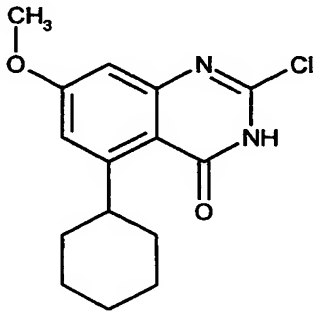
2M Sodium hydroxide solution (12.5mL, 25mmol) was added to a solution of the dichloride from preparation 16 (1.71g, 6.04mmol) in dioxane (50mL), and the solution stirred at room temperature for 8 hours. The mixture was acidifed using 2M hydrochloric acid (20mL), the resulting precipitate filtered off, washed with water, acetone and diethyl ether, and dried *in vacuo*, to afford the title compound, 1.26g.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.69-1.79 (m, 1H), 1.86-2.10 (m, 3H), 2.27-2.38 (m, 2H), 3.87 (s, 3H), 4.51 (m, 1H), 6.90 (d, 1H), 6.94 (d, 1H), 12.83 (bs, 1H).

LRMS : m/z (ES$^+$) 287 [MNa$^+$]

Preparation 20

2-Chloro-5-cyclohexyl-7-methoxy-4(3*H*)-quinazolinone



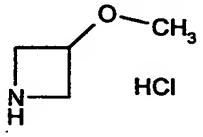
The title compound was obtained as a white solid in 96% yield, after trituration with diethyl ether, from the dichloride from preparation 17, following a similar procedure to that described in preparation 18.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.14-1.47 (m, 5H), 1.66-1.84 (m, 5H), 3.85 (s, 3H), 4.13 (m, 1H), 6.88 (d, 1H), 6.90 (d, 1H), 12.84 (bs, 1H).

LRMS : m/z (ES$^+$) 293 [MH$^+$]

Preparation 21

3-Methoxyazetidine hydrochloride

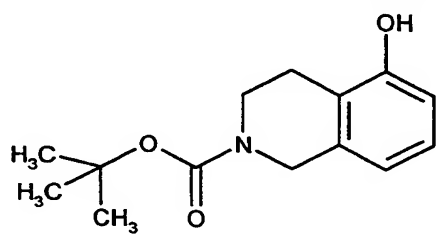


1N Ethereal hydrochloric acid was added to a solution of 1-(diphenylmethyl)-3-methoxyazetidine (WO 9613502) (1.3g, 5.14mmol) in dichloromethane (10mL), until a precipitate formed, and the mixture evaporated under reduced pressure. The residual foam was re-dissolved in methanol (75mL), 10% palladium on charcoal (900mg) and ammonium formate (6.5g) added, and the mixture heated under reflux for 30 minutes. The cooled mixture was filtered through Arbocel®, the filtrate evaporated under reduced pressure, and the residue partitioned between dichloromethane and water. The layers were separated, the aqueous phas acidifed using 1N hydrochloric acid, and the solution evaporated under reduced pressure. The residual solid was triturated with ethanol and then dichloromethane, and the solid filtered off. The filtrate was evaporated under reduced pressure to give the title compound as a yellow oil, 130mg.

^{1}H-nmr (CDCl_3, 400MHz) δ: 3.22 (bs, 3H), 3.88 (m, 2H), 4.10 (m, 2H), 4.26 (m, 1H).

Preparation 22

tert-Butyl 5-hydroxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



A solution of di-*tert*-butyl dicarbonate (66.75g, 0.31mol) was suspended in 1M sodium hydroxide solution (200mL) and 1,4-dioxane (300mL) under nitrogen gas. A solution of 1,2,3,4-tetrahydro-5-isoquinolinol (20.0g, 134mmol) in 1,4-dioxane

(100mL) was added and the resulting suspension stirred at room temperature for 16 hours. Th reaction mixture was concentrated under reduced pressure, and the residue partitioned between IM hydrochloric acid (300mL) and dichloromethane (500mL). The aqueous phase was re-extracted with dichloromethane (200mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an orange oil. The crude product was dissolved in 1,4-dioxane (200mL) and methanol (100mL) under nitrogen gas followed by the addition of 2N sodium hydroxide solution (150mL) and the resulting cloudy mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between ethyl acetate (600mL) and water (200mL). The organic phase was separated, washed with 2N hydrochloric acid (200mL), brine (250mL) then dried ($MgSO_4$) and concentrated under reduced pressure to give a tan solid. The solid was suspended in dichloromethane (150mL) then pentane added (800mL) and filtered to give the title compound as a white solid (32.04g, 84%).

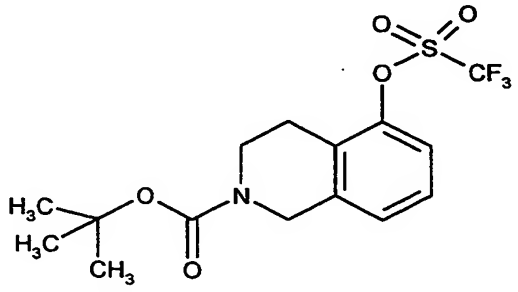
^{1}H-nmr ($CDCl_3$, 300MHz) δ: 1.49 (s, 9H), 2.76 (t, 2H), 3.66 (t, 2H), 4.56 (s, 2H), 5.29 (bs, 1H), 6.67 (dd, 2H), 7.05 (dd, 1H).

LRMS : m/z (ES^+) 272 [MNa^+].

Microanalysis: Found: C, 67.30; H, 7.68; N, 5.61. $C_{14}H_{19}NO_3$ requires C, 67.45 ; H, 7.68; N, 5.62 %

Preparation 23

tert-Butyl5-{[(trifluoromethyl)sulfonyl]oxy}-3,4-dihydro-2(1H)-isoquinolinecarboxylate



Triethylamine (20.1mL, 144mmol) was added to a suspension of the compound from preparation 22 (32.65g, 131mmol) in dichloromethane (400mL) under

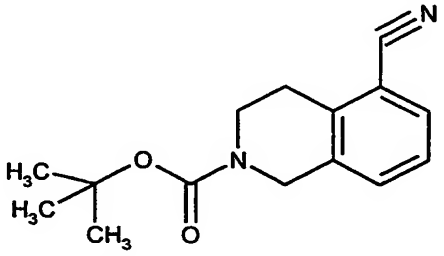
nitrogen gas. The mixture was cooled to 0°C and N-phenylbistrifluoromethanesulfonamide (51.46g, 144mmol) was added portionwise. The resulting brown solution was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was washed consecutively with water (200mL), 0.5M hydrochloric acid (200mL), brine (250mL) and then dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of n-pentane:diethyl ether (100:0 to 70:30). The product was co-evaporated with dichloromethane (2 x 100mL) to give the title compound as a colourless gum (40.1g, 80%).

^{1}H-nmr ($CDCl_3$, 300MHz) δ: 1.49 (s, 9H), 2.89 (t, 2H), 3.65 (t, 2H), 4.59 (s, 2H), 7.13 (m, 2H), 7.24 (dd, 1H).

LRMS : m/z (ES^+) 404 [MNa^+].

Preparation 24

tert-Butyl 5-cyano-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



The compound from preparation 23 (20.0g, 52mmol) was dissolved in N,N-dimethylformamide (120mL) under nitrogen gas. Zinc cyanide (6.15g, 52mmol), lithium chloride (2.22g, 52mmol) and tetrakis(triphenylphosphine)palladium (0) (2.42g, 2.1mmol) were added and the mixture heated at 110°C for 8 hours. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between dichloromethane (500mL) and saturated sodium bicarbonate solution (250mL). The aqueous phase was re-extracted with dichloromethane (300mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure to give a golden oil. The crude product was purified by column chromatography on silica gel using n-pentane:ethyl acetate (90:10) as

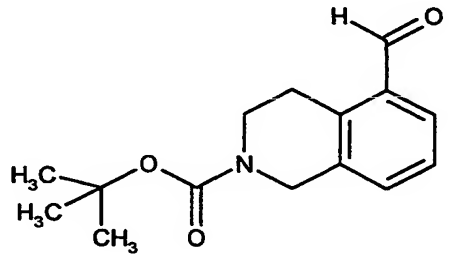
eluant. The product was co-evaporated with dichloromethane (2 x 100mL) to give the title compound as a colourless oil (13.32g, 49%).

^{1}H-nmr ($CDCl_3$, 300MHz) δ: 1.48 (s, 9H), 3.02 (t, 2H), 3.70 (t, 2H), 4.58 (s, 2H), 7.20-7.35 (m, 2H), 7.50 (d, 1H).

LRMS : m/z (ES^+) 281 [MNa^+].

Preparation 25

tert-Butyl 5-formyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



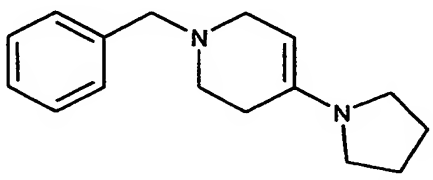
A solution of the compound from preparation 24 (9.1g, 35mmol) in toluen (100mL) was cooled to -78°C under nitrogen gas. Over 1 hour, diisobutylaluminium hydride (80 mL of a 1M solution in toluene, 80 mmol) was added dropwise keeping the internal temperature below -60°C and the resulting mixture stirred for 2 hours at -78°C. Methanol (20mL) was pre-cooled to -78°C and the added dropwise to the reaction mixture keeping the internal temperature below -60°C. Over 20 mins the reaction mixture was poured into 1N hydrochloric acid (200mL) that had been pre-cooled to 0°C. The reaction mixture was extracted with ethyl acetate (3 x 400mL) and the combined organic extracts were washed with brine (200mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was co-evaporated with dichloromethane (2 x 50mL) to give the title compound as a yellow oil (8.14g, 88%).

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 1.40 (s, 9H), 3.19 (t, 2H), 3.55 (t, 2H), 4.55 (s, 2H), 7.40 (dd, 2H), 7.47 (d, 1H), 7.70 (d, 1H).

LRMS : m/z (ES^+) 284 [MNa^+].

Preparation 26

1-Benzyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine



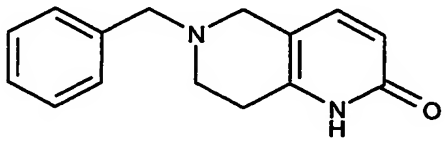
Pyrrolidine (31.8mL, 0.38mol) was added to a solution of 1-benzyl-4-piperidinone (48.0g, 0.25mol) in toluene (180mL) and the mixture refluxed under Dean-Stark conditions for 4.5 hours. The reaction mixture was allowed to cool to room

temperature and concentrated under reduced pressure to give the title compound as an orange oil (61.8g, 100%).

^{1}H-nmr (400MHz, $CDCl_3$) δ : 1.80-1.84 (m, 4H), 2.32 (m, 2H), 2.59 (t, 2H), 3.02 (4Hm,), 3.07 (s, 2H), 3.57 (s, 2H), 4.18 (s, 1H), 7.22-7.30 (m, 3H), 7.35-7.36 (d, 2H).

Preparation 27

6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2(1*H*)-one



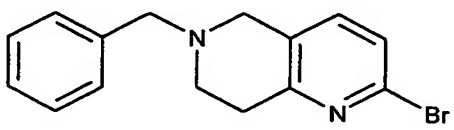
A mixture of the compound from preparation 26 (61.50g, 0.25mol) and propiolamide (J. Am. Chem. Soc. 1988; 110; 3968) (35.05g, 0.51mol) were heated under reflux in toluene (500mL) under nitrogen gas for 16 hours. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was partitioned between dichloromethane (800mL) and saturated sodium bicarbonate solution (400mL). The aqueous phase was further extracted with dichloromethane (3 x 500mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 95:05) to give the title compound as an orange solid (27.71g, 45%).

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 2.53 (t, 2H), 2.63 (t, 2H), 3.24 (s, 2H), 3.60 (s, 2H), 6.06 (d, 1H), 7.08 (d, 1H), 7.24 (m, 1H), 7.30 (m, 4H).

LRMS : m/z (ES^+) 263 [MNa^+].

Preparation 28

6-Benzyl-2-bromo-5,6,7,8-tetrahydro[1,6]naphthyridine



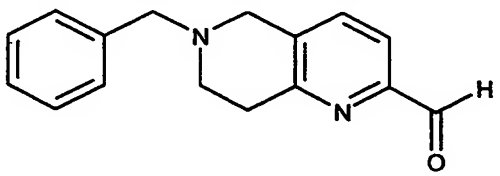
The compound from preparation 27 (9.51g, 31mmol) was susp nded in acetonitril (45mL) and anisole (45mL). Phosphorous oxybromide (44.8g, 156mmol) was added portionwise and the mixture heated for 1 hour at 120°C. The reaction was allowed to cool to room temperature and then poured onto ice (400g). Dichloromethane (400mL) was added and the mixture was then neutralised with saturated sodium carbonate solution (450mL). The organic layer was collected and the aqueous layer extracted with dichloromethane (500mL). The combined organic solutions were dried ($MgSO_4$) and concentrated und r reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 97:03) to give the title compound as a brown oil (5.79g, 61%).

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.83 (t, 2H), 3.03 (t, 2H), 3.56 (s, 2H), 3.70 (s, 2H), 7.12 (d, 1H), 7.21 (d, 1H), 7.26-7.36 (m, 5H).

LRMS : m/z (ES^+) 303 [MH^+].

Preparation 29

6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine-2-carbaldehyde



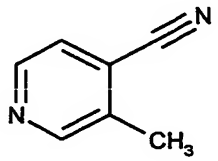
The bromide from preparation 28 (3.00g, 9.90mmol) was dissolved in tetrahydofuran (70mL) and cooled to -78°C. n-Butyl lithium (5.5mL as a 2.5M solution in hexanes, 13.8mmol) was added and the reaction stirred for a 5 minutes. N,N-Dimethylformamide (2.3mL, 29.7mmol) was then added and the reaction stirred for 1 hour, the cooling bath removed and the reaction quenched by the addition of saturated potassium dihydrogenphosphate solution (100mL). The residue was purified by flash chromatography on silica gel eluting with dichloromethane : methanol (98:2) to give the title compound as a tan solid (2.10g, 85%).

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 2.92 (m, 2H), 3.15 (m, 2H), 3.71 (s, 2H), 3.75 (s, 2H), 7.26-7.38 (m, 5H), 7.45 (d, 1H), 7.73 (d, 1H), 10.02 (s, 1H).

LRMS : m/z (ES^+) 275 [MNa^+].

Preparation 30

3-Methylisonicotinonitrile

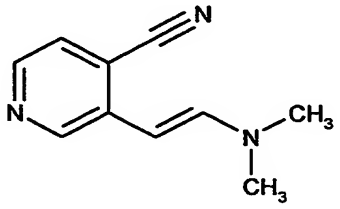


To a solution of 3-picoline N-oxide (60g, 0.55mol) in dichloromethane (1000mL) was added ethyl iodide (132mL, 1.65mol) and the mixture stirred at room temperature for 16 hours. The precipitate was collected by filtration and washed with diethyl ether (200mL) to give a white solid. The solid was dissolved in water (600mL) and warmed to 50°C. Sodium cyanide (50g, 1.02mol) was added as a solution in water (180mL) over 1 hour, keeping the internal temperature below 60°C and the resulting dark brown solution was stirred at 55°C for a further 1 hour. The reaction mixture was extracted with diethyl ether (3 x 600mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of n-pentane:dichloromethane (40:60 to 0:100). The product was co-evaporated with dichloromethane (2 x 300mL) to give the title compound as a colourless oil (30.5g, 47%).

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.55 (s, 3H), 7.47 (d, 1H), 8.60 (d, 1H), 8.67 (s, 1H).

Preparation 31

3-[(*E*)-2-(Dimethylamino)ethenyl]isonicotinonitrile



A mixture of the nitrile from preparation 30 (30.49g, 0.26mol) in N,N-dimethylformamide dimethyl acetal (200mL) and N,N-dimethylformamide (200mL) under nitrogen gas was heated under reflux for 16 hours. The reaction mixture was concentrated under reduced pressure to give a brown solid. The crude product was dissolved in dichloromethane (100mL) and n-pentane added until a precipitate formed. The solid was collected by filtration, washed with n-pentane

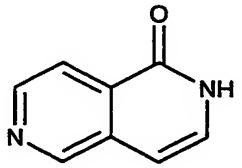
and dried under reduced pressure to give the title compound as a green solid (25.1g, 56%).

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.95 (s, 6H), 5.23 (d, 1H), 7.24 (d, 1H), 8.15 (d, 1H), 8.70 (s, 1H).

LRMS : m/z (ES^+) 174 [MH^+]

Preparation 32

[2,6]Naphthyridin-1(2*H*)-one



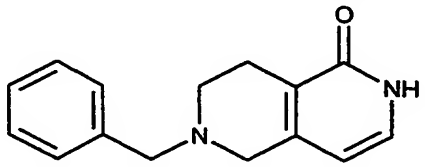
48% Hydrobromic acid (97mL, 578mmol) was added over 20 minutes, to a solution of the compound from preparation 31 (10.0g, 57.8mmol) in ethanol (100mL), and the reaction heated under reflux for 18 hours. The cooled mixture was filtered, and the collected solid was washed with ethanol (25mL), and dried *in vacuo*, to afford the title compound as fine yellow crystals, 8.54g.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 6.65 (d, 1H), 7.30 (d, 1H), 7.98 (d, 1H), 8.60 (d, 1H), 9.06 (s, 1H), 11.60 (bs, 1H).

LRMS : m/z (ES^+) 147.5 [MH^+]

Preparation 33

6-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1(2*H*)-one



To a suspension of the compound from preparation 32 (20.0g, 0.14mol) in acetonitrile (350mL) under nitrogen gas was added benzyl bromide (24.4mL, 0.21mol) and the reaction heated under reflux for 2 hours. After the reaction mixture had cooled to room temperature it was concentrated under reduced pressure to give a brown oil which was re-dissolv d in ethanol (500mL). This solution was cooled to 0°C and sodium borohydride (25.9g, 0.69mol) added

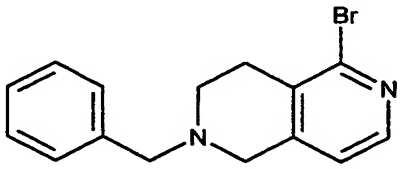
portionwis over 30 min and then stirred at 0°C for 1 hour, followed by stirring at room temperature for a further 16 hours. The reaction mixture was cooled to 0°C and 6M hydrochloric acid (200mL) was added dropwis over 30 minutes and then stirred at room temperature for 90 minutes. The resulting precipitate was filtered off, and the aqueous filtrate was basified with 2M sodium hydroxide (1000mL). With stirring, ethyl acetate (250mL) and then cyclohexane (250mL) were added and the resulting precipitate collected by filtration to give the title compound as a light yellow solid (15.50g, 53%).

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 2.27 (t, 2H), 2.60 (t, 2H), 3.28 (s, 2H), 3.62 (s, 2H), 5.87 (d, 1H), 7.10 (d, 1H), 7.21-7.25 (m, 5H), 11.23 (bs, 1H).

LRMS : m/z (ES^+) 241 [MH^+].

Preparation 34

2-Benzyl-5-bromo-1,2,3,4-tetrahydro[2,6]naphthyridine



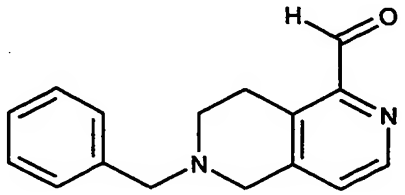
Phosphorous oxybromide (74.57g, 260mmol) was added portionwise to a suspension of the compound from preparation 33 (15.5g, 64.6mmol) anisole (200mL) and acetonitrile (100mL), and the solution stirred under reflux for 4 hours. The cooled mixture was poured onto ice (500g) and diluted with dichloromethane (500mL). The mixture was slowly neutralised using saturated sodium bicarbonate solution, the phase separated, and the aqueous layer extracted with further dichloromethane (500mL). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure to give a green oil. The crude product as purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (50:50 to 60:40), and repeated using diethyl ether:pentane (50:50) to afford the title compound as a white solid, 17.4g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.79 (m, 4H), 3.55 (s, 2H), 3.67 (s, 2H), 6.85 (d, 1H), 7.23-7.33 (m, 5H), 8.06 (d, 1H).

LRMS : m/z (ES^+) 326 [MNa^+]

Preparation 35

6-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridine-1-carbaldehyde



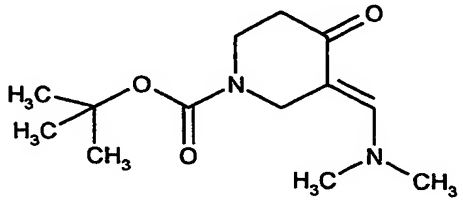
The compound from preparation 34 (3.2g, 10.6mmol) was dissolved in dry tetrahydrofuran (80mL) under nitrogen gas and cooled to -78°C. n-Butyl lithium (7.3mL as a 1.6M solution in hexanes, 11.6mmol) was added dropwise over 3 minute s and the reaction stirred for a further 3minutes. N,N-Dimethylformamide (2.5mL, 31.8mmol) was then added, the reaction stirred for 15 minutes and the cooling bath removed and the reaction stirred for a further 15 minutes before being quenched by water (20mL). The reaction mixture was partitioned betw en ethyl acetate (250mL) and water (100mL). The organic phase was separated, washed with water (100mL), brine (100mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 80:20) to give the title compound as an orange semi-solid (1.27g, 48%).

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.77 (t, 2H), 3.30 (t, 2H), 3.62 (s, 2H), 3.67 (s, 2H), 7.08 (d, 1H), 7.23-7.35 (m, 5H), 8.50 (d, 1H), 10.15 (s, 1H).

LRMS : m/z (ES^+) 275 [MNa^+]

Preparation 36

tert-Butyl-3-[(dimethylamino)methylene]-4-oxo-1-piperidinecarboxylate



Tert-butyl-4-oxo-1-piperidinecarboxylate (10g, 50mmol) and N,N-dimethylformamide dimethyl acetal (7.3mL, 55mmol) were added to N,N-dimethylformamide (75mL) under nitrogen gas and the mixture heated at 90°C for 8 hours and then stirred for a further 16 hours at room temperature. The reaction

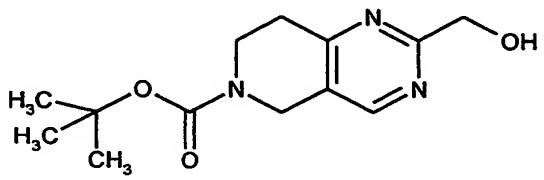
mixture was concentrated under reduced pressure, and the residue partitioned between ethyl acetate (200mL) and brine (200mL). The aqueous phase was re-extracted with ethyl acetate (200mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil that solidified on standing. Trituration with cyclohexane (20mL) gave the title compound as a light brown solid (8.5g, 67%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ :1.45 (s, 9H), 2.42 (t, 2H), 3.06 (s, 6H), 3.59 (t, 2H), 4.54 (s, 2H), 7.43 (s, 1H).

LRMS : m/z (ES^+) 277 [MNa^+].

Preparation 37

tert-Butyl 2-(hydroxymethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate

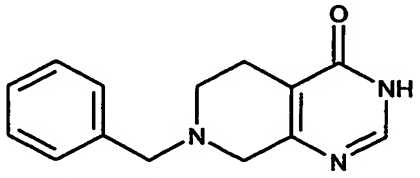


Sodium metal (414mg, 16.5mmol) was added to ethanol (42mL) and stirred at room temperature under nitrogen gas until a clear solution had formed. The compound from preparation 24 (4.2g, 16.5mmol) and 2-hydroxyethanimidamid (J. Am. Chem. Soc.; 68; 1946; 2394) (2g, 18mmol) were added and the reaction mixture heated under reflux for 3 hours and then allowed to cool to room temperature and partitioned between ethyl acetate (100mL) and saturated sodium bicarbonate solution (100mL). The aqueous phase was re-extracted with ethyl acetate (50mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil which was purified by column chromatography on silica gel eluting with a solvent gradient of ethyl acetate : methanol (100:0 to 97:03) to give the title compound as a brown oil (3.00g, 73%).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 1.49 (s, 9H), 2.95 (t, 2H), 3.46 (bs, 1H), 3.75 (t, 2H), 4.59 (s, 2H), 4.77 (d, 2H), 8.44 (s, 1H).

Preparation 38

7-B nzyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4(3*H*)-on



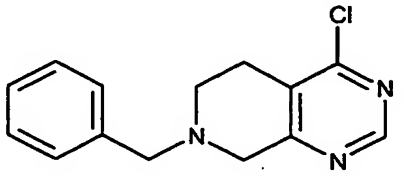
Sodium metal (10.1g, 0.44mol) was added to ethanol (520mL) and stirred at room temperature under nitrogen gas until a clear solution had formed. Ethyl-3-oxo-N-benzylpiperidine-4-carboxylate hydrochloride (56.5g, 0.19mol) and formamidine acetate (22.9g, 0.22mol) were then added and the reaction mixture heated under reflux for 40 hours. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between water (400mL) and dichloromethane (400mL). The aqueous phase was re-extracted with dichloromethane (2x100mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting solid was triturated with diethyl ether (100mL) and the product collected by filtration to give the title compound as a light brown solid (32.0g, 70%).

^{1}H-nmr (400 MHz, $CDCl_3$) δ : 2.64 (m, 2H), 2.73 (m, 2H), 3.48 (s, 2H), 3.70 (s, 2H), 7.25-7.34 (m, 5H), 7.97 (s, 1H), 12.37 (bs, 1H).

LRMS (ES^+): m/z 264 [MNa^+]

Preparation 39

7-Benzyl-4-chloro-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine



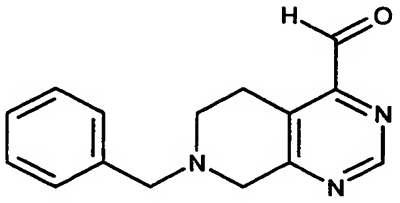
The compound from preparation 38 (11.0g, 42mmol) was mixed with phosphorous oxychloride (80mL) and heated to 90°C under nitrogen gas for 1 hour. The reaction mixture was concentrated under reduced pressure, re-dissolved in dichloromethane (100mL) and poured onto ice (100g). The mixture was stirred for 10 minutes, and then basified with saturated sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (3x150mL) and the combined

organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 90:10) to give the title compound as a brown oil (9.75g, 90%).

^{1}H-nmr (400 MHz, $CDCl_3$) δ : 2.81 (t, 2H), 2.85 (t, 2H), 3.68 (s, 2H), 3.72 (s, 2H), 7.29-7.34 (m, 5H), 8.70 (s, 1H).

Preparation 40

7-Benzyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine-4-carbaldehyde



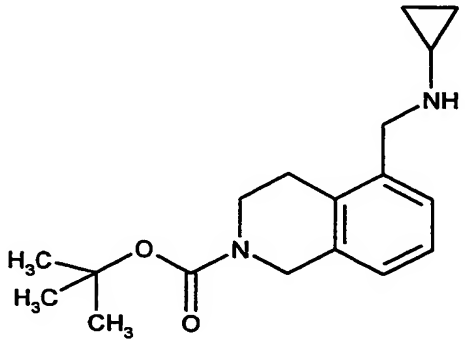
Tellurium metal (5.72g, 45mmol) was suspended in tetrahydrofuran (100mL) at room temperature under nitrogen gas and n-butyl lithium (20mL of a 2.5 M solution in hexanes, 50 mmol) added over 1 minute. This mixture was stirred for a further 15 minutes and then added to a solution of the compound from preparation 39 (9.75g, 37.5mmol) in tetrahydrofuran (100mL) and the mixture stirred for 15 minutes before being cooled to -78°C. n-Butyl lithium (20mL of a 2.5 M solution in hexanes, 50mmol) was added over 1 minute and the mixture stirred for 5 minutes before N,N-dimethylformamide (20mL) was added. The reaction was stirred for a further 30 minutes at -78°C, quenched with water (10mL) then allowed to warm to room temperature. Ethyl acetate (200mL) and water (100mL) were added, the organic layer separated and washed with brine (100mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:ethyl acetate (100:0 to 50:50) to give the title compound as a brown oil, 3.10g.

^{1}H-nmr (400MHz, $CDCl_3$): δ 2.79 (t, 2H), 3.27 (t, 2H), 3.73 (s, 2H), 3.76 (s, 2H), 7.33 (m, 5H), 9.16 (s, 1H), 10.11 (s, 1H).

LRMS (ES^+): m/z 276 [MNa^+]

Preparation 41

tert-Butyl 5-[(cyclopropylamino)methyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



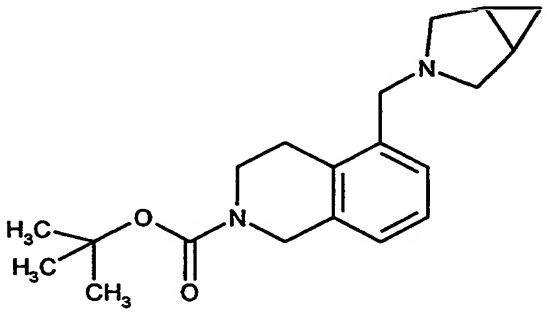
Cyclopropylamine (0.81mL, 11.4mmol) and acetic acid (0.49µl, 0.85mmol) were added to a solution of the aldehyde from preparation 25 (2.0g, 7.65mmol) in tetrahydrofuran (50mL), and the solution stirred at room temperature for 2 hours. Sodium triacetoxyborohydride (4.0-g, 19.1mmol) was added, and the reaction stirred at room temperature for 72 hours. The mixture was partitioned between 0.88 ammonia (20mL), water (25mL) and ethyl acetate (75mL). The layers were separated, the organic phase washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound as a clear oil, 2.34g.

^{1}Hnmr ($CDCl_3$, 400MHz) δ: 0.38 (m, 2H), 0.42 (m, 2H), 1.46 (s, 9H), 2.16 (m, 1H), 2.84 (t, 2H), 3.65 (t, 2H), 3.80 (s, 2H), 4.58 (s, 2H), 7.01 (m, 1H), 7.18 (m, 2H).

LRMS : m/z (ES^+) 303 [MH^+], 325 [MNa^+]

Preparation 42

tert-Butyl 5-(3-azabicyclo[3.1.0]hex-3-ylm thyl)-3,4-dihydro-2(1*H*)-isoquinolin carboxylate



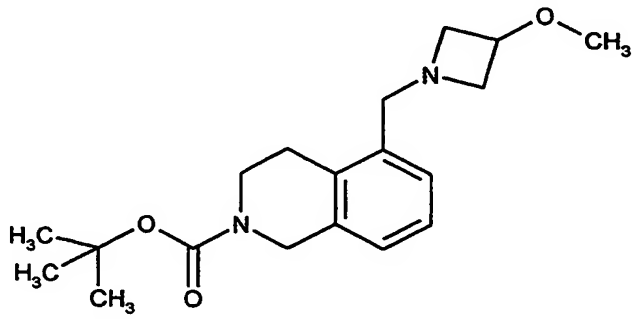
3-Azabicyclo[3.1.0]hexane hydrochloride (WO 9522547) (203mg, 1.7mmol) sodium acetate (140mg, 1.7mmol), powdered 4Å molecular sieves (500mg) and acetic acid (0.49µl, 0.85mmol) were added to a solution of the aldehyde from preparation 25 (403mg, 1.55mmol) in tetrahydrofuran (10mL), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (720mg, 3.4mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between sodium hydroxide solution (60mL, 1N) and ethyl acetate (60mL) and the layers separated. The organic phase was washed with brine (60mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate:methanol (95:5) as eluant, to give a colourless oil. This was dissolved in diethyl ether (20mL) and the solution extracted with 1N hydrochloric acid (2x20mL). The combined aqueous solutions were then basified to pH 11 using 1N sodium hydroxide solution (50mL), and this aqueous solution extracted with ethyl acetate. These combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound as a white solid, 224mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.30 (m, 1H), 0.66 (m, 1H), 1.31 (m, 2H), 1.48 (s, 9H), 2.33 (d, 2H), 2.82 (m, 4H), 3.56 (s, 2H), 3.60 (t, 2H), 4.57 (s, 2H), 6.99 (m, 1H), 7.09 (m, 2H).

LRMS : m/z (ES^+) 351 [MNa^+]

Preparation 43

tert-Butyl 5-[(3-m thoxy-1-azetidinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



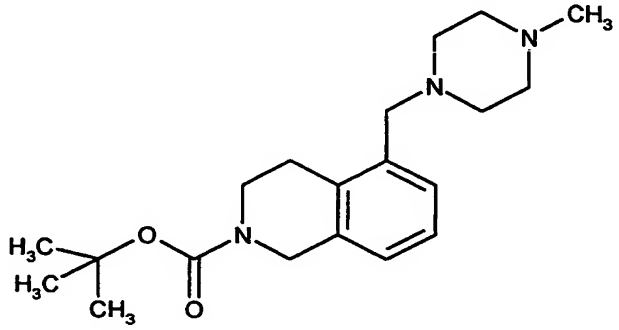
Sodium acetate (82mg, 1.0mmol) the aldehyde from preparation 25 (264mg, 1.05mmol) and acetic acid (0.07mL, 1.2mmol) were added to a solution of the amine hydrochloride from preparation 21 (130mg, 1.05mmol) in tetrahydrofuran (10mL), and the solution stirred at room temperature for 0.5 hour. Sodium triacetoxyborohydride (530mg, 2.5mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate and basified to pH 11 using 0.88 ammonia. The layers were separated, the aqueous phase extracted with ethyl acetate and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using dichloromethane:methanol (97:3) as eluant to afford the title compound as an oil, 226mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.45 (s, 9H), 2.81 (t, 2H), 2.95 (t, 2H), 3.22 (s, 3H), 3.60 (m, 6H), 4.01 (m, 1H), 4.58 (s, 2H), 7.00 (m, 1H), 7.13 (m, 2H).

LRMS : m/z (ES^+) 333.3 [MH^+]

Preparation 44

tert-Butyl 5-[(4-m thyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolin carboxylate



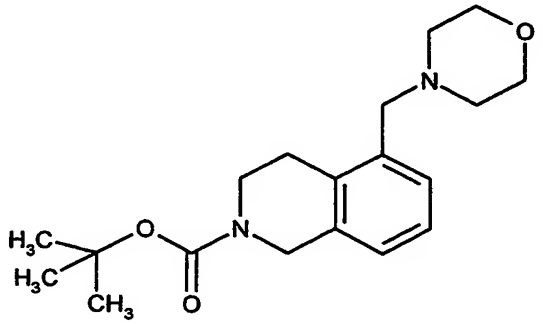
Acetic acid (0.078mL, 1.3mmol) followed by sodium triacetoxyborohydride (572mg, 2.7mmol) were added to a solution of 1-methylpiperazine (0.139mL, 1.25mmol) and the aldehyde from preparation 25 (250mg, 0.96mmol) in tetrahydrofuran (10mL), and the solution stirred at room temperature for 3 hours. The reaction was poured into 2N sodium hydroxide solution (50mL), and the mixture extracted with ethyl acetate (3x). The combined organic extracts w re washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant to afford the title compound, 201mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.46 (s, 9H), 1.75 (m, 2H), 2.25 (s, 3H), 2.42 (m, 6H), 2.90 (t, 2H), 3.43 (s, 2H), 3.63 (t, 2H), 4.55 (s, 2H), 7.01 (m, 1H), 7.14 (m, 2H).

LRMS : m/z (ES^+) 346 [MH^+]

Preparation 45

tert-Butyl 5-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



A solution of morpholine (1.34mL, 15.3mmol) and the aldehyde from preparation 25 (2.0g, 7.65mmol) in acetonitrile (40mL) was stirred at room temperature for 1.5 hours, then cooled in an ice-bath. Sodium triacetoxyborohdride (1.95g, 9.18mmol) was added portionwise, the reaction allowed to warm to room temperature and stirred for 6 hours. The reaction was diluted with water (30mL), extracted with ethyl acetate (3x50mL) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, 2.60g.

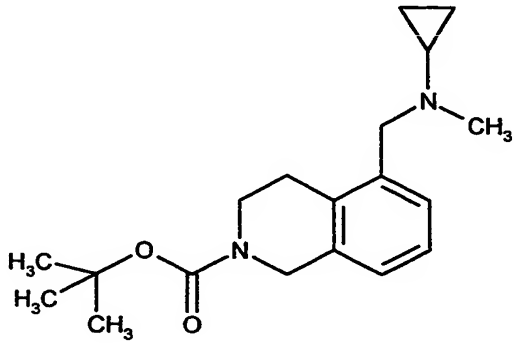
This was purified by column chromatography on silica gel using dichloromethane:diethyl ether (90:10 to 80:20) to afford the title compound as a colourless oil, 2.09g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.47 (s, 9H), 2.39 (m, 4H), 2.90 (m, 2H), 3.40 (s, 2H), 3.62 (m, 6H), 4.57 (s, 2H), 7.00 (m, 1H), 7.10 (m, 2H).

LRMS : m/z (ES^+) 355 [MNa^+]

Preparation 46

tert-Butyl 5-{[cyclopropyl(m thyl)amino]methyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



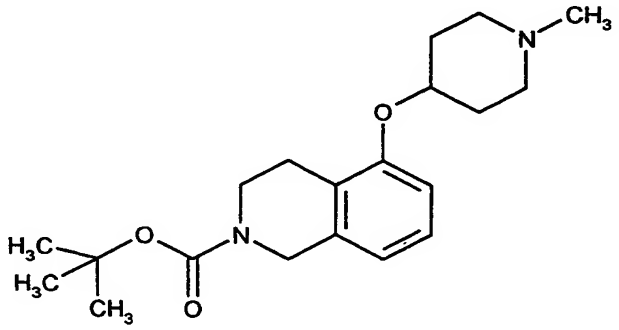
A mixture of the amine from preparation 41 (1.1g, 3.43mmol), 37% aqueous formaldehyde (1.05mL, 10.9mmol) and sodium triacetoxyborohydride (3.1g, 14.64mmol) in dichloromethane (50mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between 0.88 ammonia (15mL), water (30mL) and dichloromethane (40mL), and the layers separated. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound as a clear oil, 940mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.37 (m, 2H), 0.43 (m, 2H), 1.46 (s, 9H), 1.69 (m, 1H), 2.20 (s, 3H), 2.86 (m, 2H), 3.60 (m, 4H), 4.53 (s, 2H), 7.00 (m, 1H), 7.10 (m, 2H).

LRMS : m/z (ES^+) 317 [MH^+], 339 [MNa^+]

Preparation 47

tert-Butyl 5-[(1-methyl-4-piperidinyl)oxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



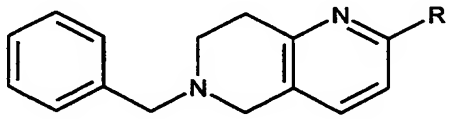
A solution of diethylazodicarboxylate (505mg, 2.9mmol) in dichloromethane (3mL) was added dropwise to a cooled (4°C) solution of the tetrahydroisoquinolinol from preparation 22 (498mg, 2mmol) and triphenylphosphine (787mg, 3mmol) in

dichloromethane (25mL) and the solution stirred at this temperature for 30 minutes. 1-Methyl-4-hydroxypiperidine (403mg, 3.5mmol) was added and the reaction stirred at room temperature for 17 hours. An additional solution of triphenylphosphine (393mg, 1.5mmol) and diethylazodicarboxylate (226mg, 1.3mmol) in dichloromethane (2mL), followed by 1-methyl-4-hydroxypiperidine (207mg, 1.8mmol) were added and the reaction stirred for a further 17 hours at room temperature. The mixture was diluted with dichloromethane (50mL), washed with water (2x75mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0.2 to 93:7:0.7) to give the title compound as a yellow oil, 466mg.

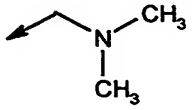
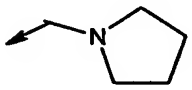
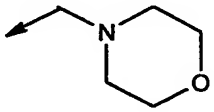
^{1}Hnmr ($CDCl_3$, 400MHz) δ: 1.48 (s, 9H), 1.86 (m, 2H), 1.97 (m, 2H), 2.29 (s, 3H), 2.32 (m, 2H), 2.61 (m, 2H), 2.77 (t, 2H), 3.63 (t, 2H), 4.34 (m, 1H), 4.54 (s, 2H), 6.69 (d, 2H), 7.09 (dd, 1H).

LRMS : m/z (ES^+) 347 [MH^+]

Preparations 48 to 50

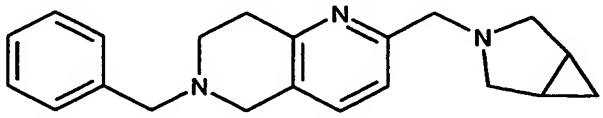


Acetic acid (2.5-3.5eq) followed by the appropriate amine (1.1-1.7eq) were added to a solution of the aldehyde from preparation 29 (1eq) in tetrahydrofuran (5mL per mmol) and the solution stirred for 15 minutes. Sodium triacetoxyborohydride (2-2.3 eq) was added, and the reaction stirred at room temperature for 17 hours. 2N hydrochloric acid was added, to give a pH of 1, the mixture stirred for 15 minutes, then re-basified to pH 12 using 2N sodium hydroxide solution. The mixture was extracted with dichloromethane, the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0.5 to 90:10:1) to afford the desired compound.

Prep	R	Yield	Data
48		76 yellow gum	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.25 (s, 6H), 2.83 (t, 2H), 3.01 (t, 2H), 3.54 (s, 2H), 3.60 (s, 2H), 3.70 (s, 2H), 7.15 (d, 1H), 7.23 (m, 2H), 7.35 (m, 4H). LRMS : m/z (ES^+) 304 [MNa^+]
49		86 yellow oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.77 (m, 4H), 2.55 (m, 4H), 2.83 (t, 2H), 3.03 (t, 2H), 3.59 (s, 2H), 3.69 (s, 2H), 3.72 (s, 2H), 7.14-7.38 (m, 7H). LRMS : m/z (ES^+) 308 [MH^+]
50		73 yellow oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.49 (m, 4H), 2.84 (t, 2H), 3.03 (t, 2H), 3.59 (m, 4H), 3.70 (m, 6H), 7.16-7.38 (m, 7H). LRMS : m/z (ES^+) 346 [MNa^+]

Preparation 51

2-(3-Azabicyclo[3.1.0]hex-3-ylmethyl)-6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine



3-Azabicyclo[3.1.0]hexane hydrochloride (WO 9522547) (300mg, 2.49mmol), sodium acetate (223mg, 2.71mmol) and acetic acid (0.8mL) were added to a solution of the aldehyde from preparation 29 (570mg, 2.26mmol) in tetrahydrofuran (15mL) and dichloromethane (10mL), and the solution stirred at room temperature for 0.5 hour. Sodium triacetoxyborohydride (960mg, 4.52mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between sodium hydroxide solution (60mL, 1N) and ethyl acetate (60mL) and the layers separated. The organic phase was washed with brine

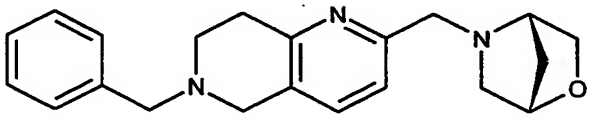
(60mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethan :methanol:0.88 ammonia (95:5:0.5) as eluant, to give the title compound as a yellow oil, 375mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ : 0.30 (m, 1H), 0.62 (m, 1H), 1.35 (m, 2H), 2.35 (m, 2H), 2.76 (m, 2H), 2.88 (m, 4H), 3.52 (s, 2H), 3.57 (s, 2H), 3.64 (s, 2H), 7.03 (d, 1H), 7.30 (m, 6H).

LRMS : m/z (ES^+) 320 [MH^+]

Preparation 52

(1*S*,4*S*)-5-[(6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)methyl]-2-oxa-5-azabicyclo[2.2.1]heptane



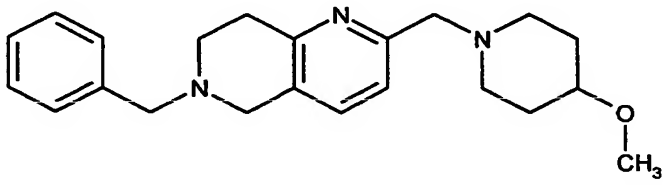
A mixture of the aldehyde from preparation 29 (866mg, 3.44mmol), 1S,4S-2-aza-5-oxabicyclo[2.2.1]heptane hydrochloride (700mg, 5.16mmol), sodium acetate (423mg, 5.16mmol) and acetic acid (310mg, 5.16mmol) in tetrahydrofuran (20mL) was stirred at room temperature for 2 hours. 2M Hydrochloric acid (20mL) was added cautiously, the mixture stirred for 10 minutes, then the mixture basifi d using 1N sodium hydroxide solution. The mixture was extracted with dichloromethane (3x60mL), the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 90:10) to afford the title compound as a yellow oil, 783mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.79 (m, 1H), 1.99 (m, 1H), 2.69 (m, 1H), 2.86 (t, 2H), 2.93 (m, 1H), 3.03 (t, 2H), 3.52 (m, 1H), 3.62 (s, 2H), 3.66 (m, 1H), 3.72 (s, 2H), 3.89 (m, 2H), 4.16 (m, 1H), 4.44 (m, 1H), 7.21-7.83 (m, 7H).

LRMS : m/z ($APCI^+$) 336 [MH^+]

Preparation 53

6-Benzyl-2-[(4-methoxy-1-piperidinyl)methyl]-5,6,7,8-tetrahydro[1,6]naphthyridine



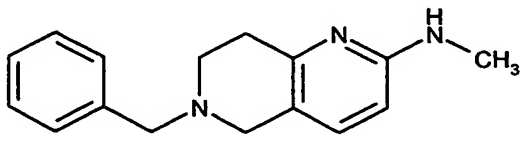
Triethylamine (0.43mL, 3.2mmol) followed by the aldehyde from preparation 29 (750mg, 3.0mmol) was added to a solution of the piperidine hydrochloride from preparation 94 (483mg, 3.2mmol) in tetrahydrofuran (20mL), and the solution stirred for 1 hour. Sodium triacetoxyborohydride (745mg, 3.5mmol) was added portionwise, and the reaction stirred at room temperature for 18 hours. 2N Hydrochloric acid (4mL) was added, the solution stirred for 5 minutes, then poured into water (80mL), and the pH adjusted to 9 using 2N sodium hydroxide solution. The mixture was extracted with dichloromethane (3x100mL), the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) to afford the title compound as an oil, that crystallised on standing, 710mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 1.40 (m, 2H), 1.80 (m, 2H), 2.10 (m, 2H), 2.62 (m, 2H), 2.76 (m, 2H), 2.82 (m, 2H), 3.16 (m, 1H), 3.20 (s, 3H), 3.46 (s, 2H), 3.54 (s, 2H), 3.64 (s, 2H), 7.16 (2xs, 2H), 7.20-7.40 (m, 5H).

LRMS : m/z (ES^+) 352 [MH^+]

Preparation 54

N-(6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)-*N*-methylamine



Liquid methylamine (20mL) was added to a cooled (-70°C) solution of 6-benzyl-2-chloro-5,6,7,8-tetrahydro[1,6]naphthyridine (WO 9830560) (5.5g, 21.25mmol) in methanol (30mL). The mixture was heated to 140°C in a sealed vessel for 72 hours, then cooled. The reaction mixture was evaporated under reduced pressure

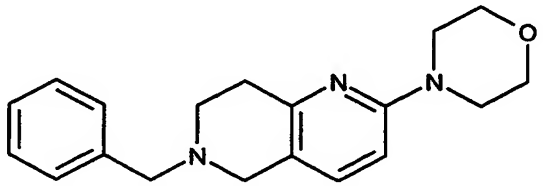
and the residual brown oil purifi d by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0 to 96:4:0.5) to afford the title compound as a white solid, 2.97g

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.80 (m, 4H), 2.87 (s, 3H), 3.49 (s, 2H), 3.68 (s, 2H), 4.36 (bs, 1H), 6.19 (d, 1H), 7.05 (d, 1H), 7.24 (m, 1H), 7.31 (m, 2H), 7.36 (m, 2H).

LRMS : m/z (ES^+) 254 [MH^+]

Preparation 55

6-Benzyl-2-(4-morpholinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine



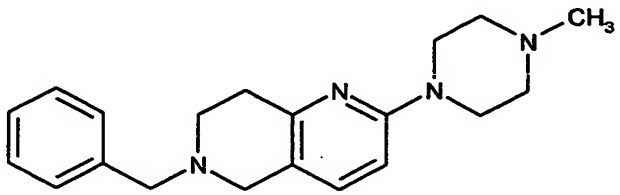
Morpholine (0.33mL, 3.7mmol), sodium *tert*-butoxide (337mg, 3.7mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (124mg, 0.2mmol) and tris(dibenzylideneacetone)dipalladium (0) (92mg, 0.1mmol) were added sequentially to a solution of the bromide from preparation 28 (763mg, 2.5mmol) in toluene (10mL), and the solution purged with nitrogen. The reaction was then stirred at 100°C for 18 hours, cooled and filtered through silica gel, washing through with a solution of dichloromethane:methanol. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 95:5) to afford the title compound.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.79 (m, 2H), 2.81 (m, 2H), 3.41 (m, 4H), 3.46 (s, 2H), 3.67 (s, 2H), 3.78 (m, 4H), 6.41 (d, 1H), 7.12 (s, 1H), 7.30 (m, 5H).

LRMS : m/z (ES^+) 310 [MH^+]

Preparation 56

6-Benzyl-2-(4-methyl-1-pip razinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine



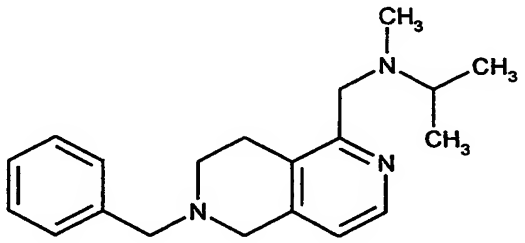
The title compound was obtained in 36% yield, from the bromide from preparation 28 and 1-methylpiperazine, following the procedure described in preparation 55.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.30 (s, 3H), 2.49 (m, 4H), 2.79 (m, 2H), 2.82 (m, 2H), 3.49 (m, 6H), 3.08 (s, 2H), 6.42 (d, 1H), 7.09 (d, 1H), 7.35 (m, 5H).

LRMS : m/z (ES^+) 345 [MNa^+]

Preparation 57

N-[(6-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)methyl]-*N*-methyl-2-propanamine



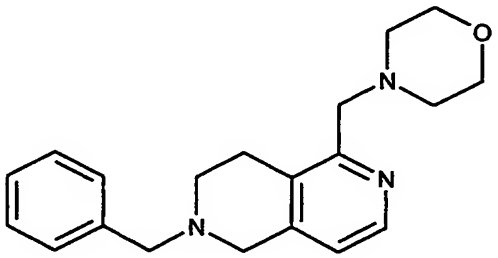
N-Isopropyl-N-methylamine (330μl, 3.15mmol) followed by acetic acid (132μl, 2.31mmol) were added to a solution of the aldehyde from preparation 35 (530mg, 2.1mmol) in tetrahydrofuran (15mL), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (1.11g, 5.26mmol) was then added, and the reaction stirred for 18 hours. The reaction mixture was partitioned between 1N sodium hydroxide solution (30mL), and ethyl acetate (30mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (30mL) and the combined organic extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give an oil. This was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 90:10:1) to afford the title compound as a yellow oil, 272mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.06 (d, 6H), 2.13 (s, 3H), 2.77 (t, 2H), 2.85 (m, 1H), 2.99 (t, 2H), 3.58 (s, 2H), 3.62 (s, 2H), 3.66 (s, 2H), 6.78 (m, 1H), 7.35 (m, 5H), 8.23 (m, 1H).

LRMS : m/z (ES^+) 310 [MH^+]

Preparation 58

2-Benzyl-5-(4-morpholinylmethyl)-1,2,3,4-tetrahydro[2,6]naphthyridine



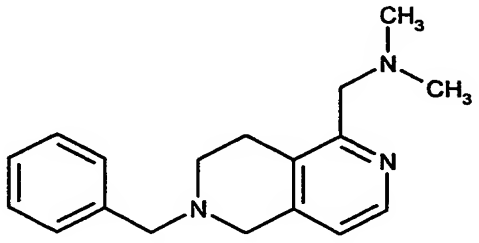
The title compound was obtained as a yellow oil, from the aldehyde from preparation 35 and morpholine, following a similar procedure to that described in preparation 57.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.42 (m, 4H), 2.79 (m, 2H), 2.99 (m, 2H), 3.57-3.78 (m, 10H), 6.80 (d, 1H), 7.20-7.39 (m, 5H), 8.22 (d, 1H).

LRMS m/z (ES^+) 346 [MNa^+]

Preparation 59

(6-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)-*N*,*N*-dimethylmethanamine



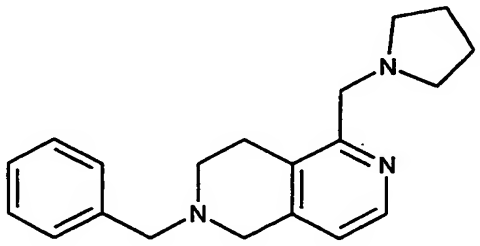
Dimethylamine (2mL, 2M in tetrahydrofuran, 4mmol) followed by acetic acid (480mg, 8mmol) were added to a solution of the aldehyde from preparation 35 (756mg, 3mmol) in tetrahydrofuran (15mL), and the solution stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (1.27g, 6mmol) was then added, and the reaction stirred for 3 hours. The reaction was quenched by

the addition of 2N hydrochloric acid, this solution stirred for 15 minutes, basified using 1N sodium hydroxide solution, then extracted with dichloromethan (3x50mL). The combined organic extracts were dried ($MgSO_4$), and evaporated under reduced pressure to afford the title compound as an oil, 942mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.23 (s, 6H), 2.79 (m, 2H), 2.98 (m, 2H), 3.50 (s, 2H), 3.59 (s, 2H), 3.64 (s, 2H), 6.80 (d, 1H), 7.21-7.39 (m, 5H), 8.25 (d, 1H).

Preparation 60

2-Benzyl-5-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro[2,6]naphthyridine



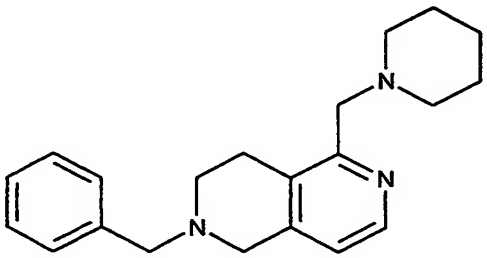
The title compound was obtained in 73% yield from the aldehyde from preparation 35 and pyrrolidine, following a similar procedure described in preparation 59, except the reaction was worked up using ethyl acetate and 0.88 ammonia.

1H-nmr ($CDCl_3$, 400MHz) δ: 1.76 (m, 4H), 2.55 (m, 4H), 2.78 (m, 2H), 2.97 (m, 2H), 3.58 (s, 2H), 3.67 (s, 2H), 3.70 (s, 2H), 6.79 (d, 1H), 7.30 (m, 5H), 8.26 (d, 1H).

LRMS : m/z (ES^+) 308 [MH^+]

Preparation 61

2-Benzyl-5-(1-piperidinylmethyl)-1,2,3,4-tetrahydro[2,6]naphthyridine



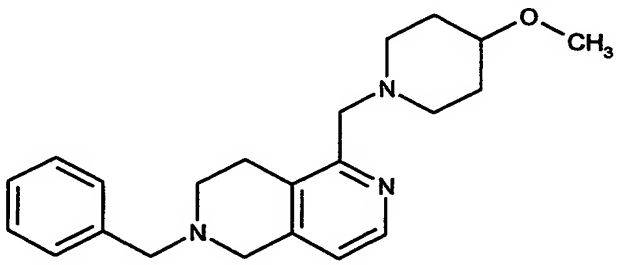
The title compound was obtained in 68% yield from the aldehyde from preparation 35 and piperidine, following a similar procedure to that described in preparation 60.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.40 (m, 2H), 1.50 (m, 4H), 2.40 (m, 4H), 2.77 (m, 2H), 3.00 (m, 2H), 3.52 (s, 2H), 3.59 (s, 2H), 3.67 (s, 2H), 6.79 (d, 2H), 7.25-7.38 (m, 5H), 8.24 (d, 1H).

HRMS : m/z (ES^+) 322.2283 [MH^+] $C_{21}H_{27}N_3$- 322.2278 [MH^+]

Preparation 62

2-Benzyl-5-[(4-methoxy-1-piperidinyl)methyl]-1,2,3,4-tetrahydro[2,6]naphthyridine



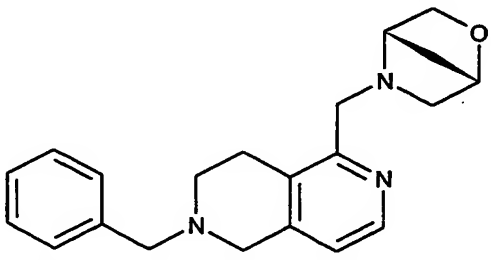
The title compound was obtained as an orange oil from the aldehyde from preparation 35 and 4-methoxypiperidine hydrochloride from preparation 94, following a similar procedure to that described in preparation 60.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.58 (m, 2H), 1.85 (m, 2H), 2.22 (m, 2H), 2.77 (m, 4H), 2.99 (m, 2H), 3.19 (m, 1H), 3.32 (s, 3H), 3.60 (m, 4H), 3.69 (s, 2H), 6.80 (d, 1H), 7.20-7.40 (m, 5H), 8.22 (d, 1H).

LRMS : m/z (ES^+) 352 [MH^+]

Preparation 63

(1*S*,4*S*)-5-[(6-benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)methyl]-2-oxa-5-azabicyclo[2.2.1]heptane



(1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptane hydrochloride (344mg, 2.54mmol), followed by sodium acetate (152mg, 1.86mmol) and acetic acid (0.1mL, 1.86mmol) were added to a solution of the aldehyde from preparation 35 (427mg,

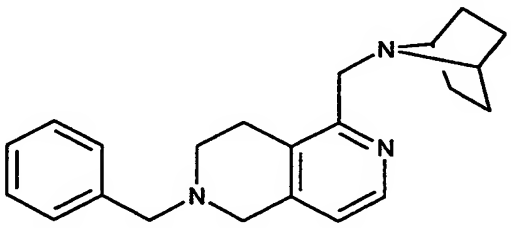
1.69mmol) in tetrahydrofuran (15mL), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (897mg, 4.23mmol) was added and th reaction stirred at room temperature for 18 hours. Th mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (50mL) and 0.88 ammonia (50mL), the layers separated, and the aqueous phase further extracted with ethyl acetate (50mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 95:5) to afford the title compound as a yellow oil, 324mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.68 (d, 1H), 1.88 (d, 1H), 2.65 (d, 1H), 2.78 (m, 2H), 2.89 (d, 1H), 2.97 (m, 2H), 3.40 (s, 1H), 3.59 (s, 2H), 3.65 (m, 3H), 3.80 (dd, 2H), 4.06 (d, 1H), 4.38 (s, 1H), 6.79 (d, 1H), 7.30 (m, 5H), 8.22 (d, 1H).

LRMS : m/z (ES^+) 358 [MNa^+]

Preparation 64

5-(7-Azabicyclo[2.2.1]hept-7-ylmethyl)-2-benzyl-1,2,3,4-tetrahydro[2,6]naphthyridine



Diisopropylethylamine (720μl, 4.13mmol) was added to a solution of 7-azabicyclo[2.2.1]heptane (Can. J. Chem. 1970; 48(13); 2065) (500mg, 3.75mmol) in dichloromethane (7mL), and the solution stirred for 40 minutes. A solution of the aldehyde from preparation 35 (650mg, 2.57mmol) in dichloromethane (2mL) was added, followed by acetic acid (300μl, 5.16mmol), and the solution stirred for a further 2 hours. Sodium triacetoxyborohydride (1.1g, 5.16mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was quenched by the addition of 2N hydrochloric acid (3mL), then basified using 1N sodium hydroxide solution (20mL). The mixture was extracted with dichloromethane (2x),

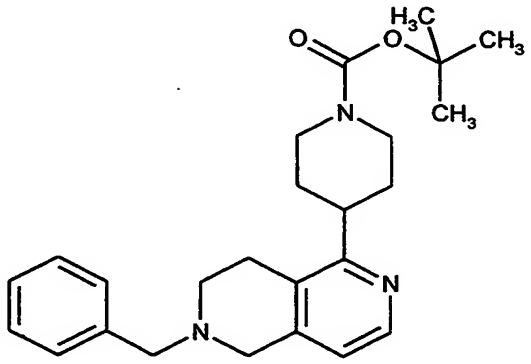
the combined organic extracts dried (Na_2SO_4) and evaporated under reduced pressure. The crud product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 94:5:1) to afford the title compound as a brown oil.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.25 (m, 4H), 1.80 (m, 4H), 2.78 (t, 2H), 3.05 (t, 2H), 3.25 (m, 2H), 3.58 (s, 2H), 3.61 (m, 2H), 3.67 (s, 2H), 6.79 (d, 1H), 7.30 (m, 5H), 8.22 (d, 1H).

LRMS : m/z (ES^+) 334 [MH^+]

Preparation 65

tert-Butyl 4-(6-benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)-1-piperidinecarboxylate



Zinc (809mg, 12.4mmol) was stirred in 1N hydrochloric acid (5mL) for 5 minutes, the mixture filtered, and the collected zinc washed with water, ethanol and diethyl ether, then dried at 100°C for 5 hours.

Dibromoethane (28µl, 0.33mmol) was added to a suspension of the zinc in N,N-dimethylformamide (12mL), and the mixture heated at 50°C for 4 minutes, then cooled. Trimethylsilyl chloride (54mg, 0.50mmol) was added, the mixture again heated at 50°C for 5 minutes, *tert*-butyl 4-iodo-1-piperidinecarboxylate (EP 1078928) (2.57g, 8.25mmol) added and stirring continued for 5 minutes. A solution of the bromide from preparation 34 (1.0g, 3.3mmol) in N,N-dimethylformamide (2.5mL), tris(dibenzylideneacetone)dipalladium (0) (38mg, 0.07mmol) and tri(o-furyl)phosphine (31mg, 0.13mmol) were added, and the reaction mixture heated at 60°C for 1 hour. The cooled mixture was partitioned between dichloromethane (50mL) and water (20mL), and the phases separated.

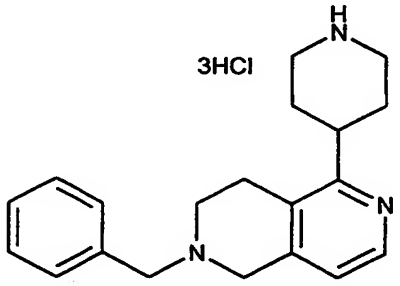
The aqu ous layer was extracted with further dichloromethane (2x50mL), and the combined organic extracts were dried ($MgSO_4$), filtered through Arbocel® and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 96:4) to give the title compound, as an oil, 1.01g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.45 (s, 9H), 1.65 (m, 2H), 1.85 (m, 4H), 2.78 (m, 4H), 2.86 (m, 2H), 3.02 (m, 1H), 3.58 (s, 2H), 3.67 (s, 2H), 6.74 (d, 1H), 7.24-7.37 (m, 5H), 8.25 (d, 1H).

LRMS : m/z (ES^+) 408 [MH^+]

Preparation 66

2-Benzyl-5-(4-piperidinyl)-1,2,3,4-tetrahydro[2,6]naphthyridine trihydrochloride



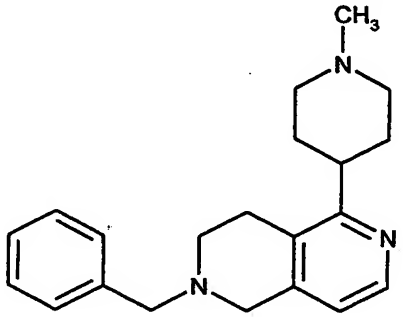
A solution of the protected amine from preparation 65 (990mg, 2.43mmol) in dry dichloromethane (30mL) was cooled in an ice/acetone bath and hydrogen chloride gas bubbled through, until saturation. The solution was stirred for a further 2 hours, then evaporated under reduced pressure to afford the title compound as a cream foam, 924mg.

^{1}H-nmr (CD_3OD, 400MHz) δ: 1.74 (m, 1H), 2.00 (m, 1H), 2.20 (m, 4H), 3.09 (m, 1H), 3.29 (m, 2H), 3.45 (m, 2H), 3.56 (m, 2H), 4.60 (s, 2H), 4.67 (s, 2H), 7.53 (m, 3H), 7.68 (m, 3H), 8.58 (d, 1H).

LRMS : m/z (ES^+) 308 [MH^+]

Preparation 67

2-Benzyl-5-(1-methyl-4-piperidinyl)-1,2,3,4-tetrahydro[2,6]naphthyridin



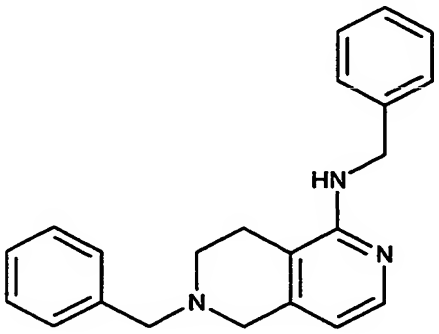
Triethylamine (675µl, 4.81mmol) was added to a solution of the amine from preparation 66 (914mg, 2.40mmol) in acetonitrile (10mL), followed by dropwise addition of formaldehyde (37% aq, 390mg, 4.81mmol), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (2.546g, 12.02mmol) was added portionwise and the reaction stirred at room temperature for 72 hours. The mixture was diluted with water (10mL), then neutralised using sodium bicarbonate solution and extracted with 5% methanol in dichloromethane solution (3x30mL). The combined organic extracts were evaporated under reduced pressure and the residual orange oil, purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (96:4:0 to 90:10:0.5) to give the title compound as an orange oil, 690mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.77 (m, 2H), 2.07 (m, 4H), 2.33 (s, 3H), 2.77 (m, 3H), 2.84 (t, 2H), 3.01 (m, 2H), 3.57 (s, 2H), 3.67 (s, 2H), 6.72 (d, 1H), 7.25-7.35 (m, 5H), 8.27 (d, 1H).

LRMS : m/z (ES^+) 322 [MH^+]

Preparation 68

N,6-Dibenzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-amin



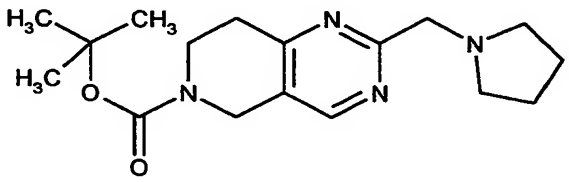
A mixture of the bromide from preparation 34 (303mg, 1mmol) and benzylamine (3mL) was stirred at 160°C for 12 hours. The cooled mixture was poured into ethyl acetate, washed with water, then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:ethyl acetate (100:0 to 60:40) to afford the title compound as a pale yellow oil, 249mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ : 2.42 (t, 2H), 2.80 (t, 2H), 3.54 (s, 2H), 3.66 (s, 2H), 4.26 (m, 1H), 4.67 (d, 2H), 6.29 (d, 1H), 7.20-7.40 (m, 10H), 7.94 (d, 1H).

LRMS : m/z (ES^+) 330 [MH^+]

Preparation 69

tert-Butyl 2-(1-pyrrolidinylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



Triethylamine (0.36mL, 2.6mmol), followed by methanesulphonyl chloride (0.22mL, 2.9mmol) were added to an ice-cold solution of the alcohol from preparation 37 (600mg, 2.4mmol) in dichloromethane (6mL), and the solution stirred at room temperature for 3 hours. The mixture was evaporated under reduced pressure, and the residue re-dissolved in tetrahydrofuran (6mL). Pyrrolidine (0.99mL, 11.9mmol) was added, and the reaction stirred at room

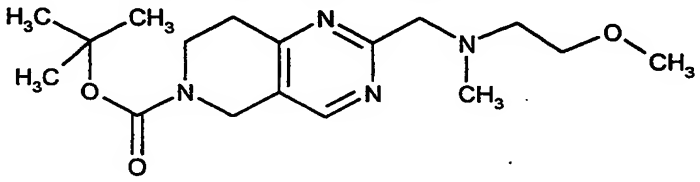
temperature for 18 hours. The mixture was partitioned between dichloromethane (50mL) and water (50mL), the layers separated and th organic phase dri d ($MgSO_4$) and evaporated under reduced pressure. The residual y llow oil was purified by column chromatography using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.2 to 95:5:0.5) to afford the title compound, 600mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 1.49 (s, 9H), 1.81 (m, 4H), 2.65 (m, 4H), 2.95 (t, 2H), 3.73 (t, 2H), 3.87 (s, 2H), 4,56 (s, 2H), 8.42 (s, 1H).

LRMS : m/z (ES^+) 319 [MH^+]

Preparation 70

tert-Butyl 2-{[(2-methoxyethyl)(methyl)amino]methyl}-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



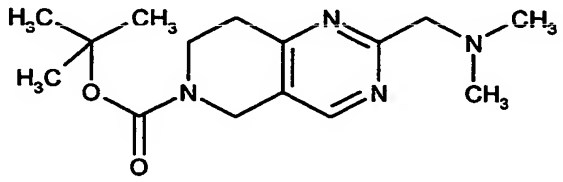
Diisopropylethylamine (388mg, 3mmol) was added to an ice-cold solution of the alcohol from preparation 37 (530mg, 2mmol) in dichloromethane (10mL). Methanesulphonyl chloride (267mg, 2.33mmol) was added, and the reaction stirred at room temperature for 1 hour. 2-Methoxyethylmethylamine (890mg, 10mmol) was added and the reaction stirred at room temperature for a further 18 hours. The mixture was poured into water, then extracted with dichloromethan (3x40mL), the combined organic extracts dried ($MgSO_4$) and evaporated und r reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 97:3) to afford the title compound as a yellow oil, 285mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.49 (s, 9H), 2,40 (s, 3H), 2,75 (t, 2H), 2,95 (t, 2H), 3.34 (s, 3H), 3.58 (t, 2H), 3.76 (t, 2H), 3.83 (s, 2H), 4.59 (s, 2H), 8.42 (s, 1H).

LRMS : m/z (ES^+) 359 [MNa^+]

Preparation 71

tert-Butyl 2-[(dimethylamino)methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



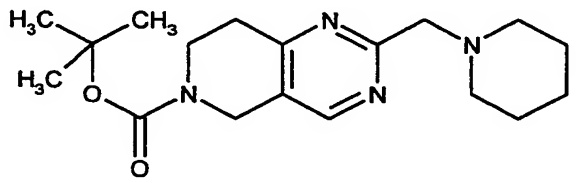
The title compound was obtained as an orange oil, from the alcohol from preparation 37 and dimethylamine (2M in tetrahydrofuran), using a similar procedure to that described in preparation 70.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.49 (s, 9H), 2.38 (s, 6H), 2.98 (t, 2H), 3.66 (s, 2H), 3.74 (t, 2H), 4.58 (s, 2H), 8.44 (s, 1H).

LRMS : m/z (ES^+) 315 [MNa^+]

Preparation 72

tert-Butyl 2-(1-piperidinylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



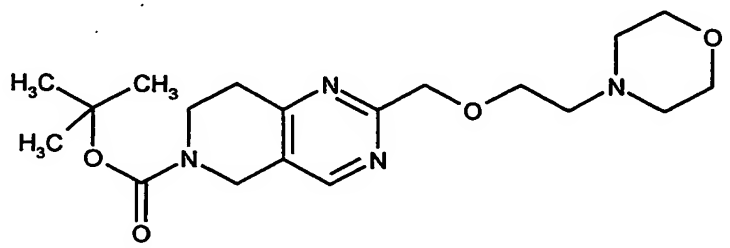
The title compound was obtained as a yellow oil in 54% yield from the alcohol from preparation 37 and piperidine, using a similar method to that described in preparation 70.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.44 (m, 11H), 1.60 (m, 4H), 2.45 (m, 4H), 2.97 (t, 2H), 3.74 (m, 4H), 4.58 (s, 2H), 8.44 (s, 1H).

LRMS : m/z (ES^+) 355 [MNa^+]

Preparation 73

tert-Butyl 2-{[2-(4-morpholinyl)ethoxy]methyl}-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



Triethylamine (305µl, 2.19mmol) and methanesulphonyl chloride (185µl, 2.39mmol) were added to an ice-cold solution of the alcohol from preparation 37 (500mg, 1.99mmol) in dichloromethane (5mL), and the solution stirred at room temperature for 2 hours.

4-(2-Hydroxyethyl)morpholine (730µl, 5.98mmol) was added dropwise to an ice-cooled suspension of sodium hydride (265mg, 60% dispersion in mineral oil, 6.57mmol) in tetrahydrofuran (5mL), and once addition was complete, the mixture was stirred at room temperature for 1.5 hours.

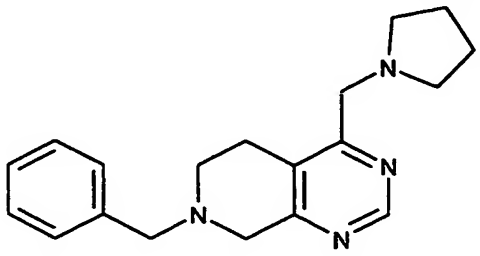
The first solution was concentrated under reduced pressure, the residual yellow oil redissolved in tetrahydrofuran (2mL), and the prepared solution of 2-hydroxyethylmorpholine anion, added dropwise. The resulting mixture was stirred at room temperature for 18 hours, then partitioned between water (30mL) and dichloromethane (30mL). The layers were separated, the aqueous phase extracted with further dichloromethane (30mL), and the combined organic solutions dried (Na_2SO_4) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (98:2:1) as eluant to afford the title compound as a yellow oil, 600mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.49 (s, 9H), 2.52 (m, 4H), 2.68 (t, 2H), 2.95 (t, 2H), 3.60 (m, 2H), 3.75 (m, 6H), 4.58 (s, 2H), 4.71 (s, 2H), 8.45 (s, 1H).

LRMS : m/z (ES^+) 401 [MNa^+]

Preparation 74

7-Benzyl-4-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine



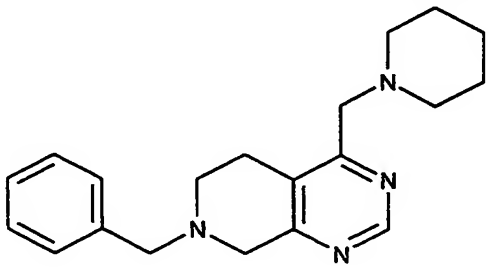
Pyrrolidine (322mg, 4.54mmol) and acetic acid (420mg, 7mmol) were added to a solution of the aldehyde from preparation 40 (574mg, 2.27mmol) in tetrahydrofuran (25mL), and the solution stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (1.48g, 7mmol) was added, and the reaction stirred for a further 4 hours. The mixture was basified using saturated sodium bicarbonate solution, and extracted using dichloromethane (3x50mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified using column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 85:5) to afford the title compound as a yellow oil, 401mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.78 (m, 4H), 2.59 (m, 4H), 2.78 (t, 2H), 2.91 (t, 2H), 3.68 (s, 2H), 3.69 (s, 2H), 3.71 (s, 2H), 7.25-7.35 (m, 5H), 8.87 (s, 1H).

LRMS : m/z (ES^+) 309 [MH^+]

Preparation 75

7-Benzyl-4-(1-piperidinylmethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine

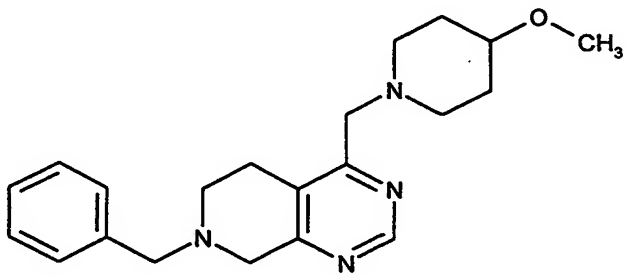


The title compound was obtained as colourless crystals in 52% yield from the aldehyde from preparation 40 and piperidine, following a similar procedure to that described in preparation 74.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.43 (m, 2H), 1.56 (m, 4H), 2.40 (m, 4H), 2.77 (t, 2H), 2.95 (t, 2H), 3.49 (s, 2H), 3.68 (s, 2H), 3.71 (s, 2H), 7.35 (m, 5H), 8.86 (s, 1H).
LRMS : m/z (ES^+) 345 [MNa^+]

Preparation 76

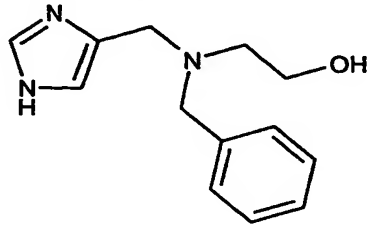
7-Benzyl-4-[(4-methoxy-1-piperidinyl)methyl]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine



The title compound was obtained as a yellow oil in 44% yield, from the aldehyde from preparation 40 and the amine hydrochloride from preparation 94, following a similar procedure to that described in preparation 74, except, 1.2eq of diisopropylethylamine was also used in the reaction.
^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.56 (m, 2H), 1.88 (m, 2H), 2.22 (m, 2H), 2.70 (m, 2H), 2.77 (t, 2H), 2.94 (t, 2H), 3.22 (m, 1H), 3.32 (s, 3H), 3.52 (s, 2H), 3.68 (s, 2H), 3.71 (s, 2H), 7.25-7.36 (m, 5H), 8.86 (s, 1H).
LRMS : m/z (ES^+) 375 [MNa^+]

Preparation 77

2-[Benzyl(1*H*-imidazol-4-ylmethyl)amino]ethanol



A suspension of 4-imidazolecarboxaldehyde (14g, 145.7mmol) and N-benzylethanolamine (26.4g, 174.8mmol) in tetrahydrofuran (200mL) was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (37.06g, 174.8mmol) was added portionwise over 40 minutes, and the reaction stirred at room

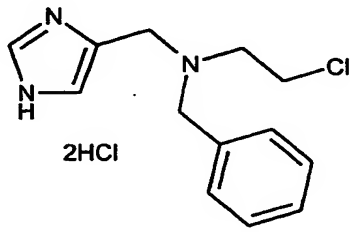
temperature for 18 hours. The reaction was quenched by the addition of water (150mL), the mixture neutralised using saturated sodium bicarbonate solution, and then extracted with dichloromethan (3x300mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. This was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0 to 90:10:1) to afford the title compound, 18.1g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.73 (t, 2H), 3.63 (t, 2H), 3.67 (s, 2H), 3.71 (s, 2H), 6.88 (s, 1H), 7.25-7.31 (m, 5H), 7.57 (s, 1H).

LRMS : m/z (ES^-) 230 $[M-H]^-$

Preparation 78

N-Benzyl-*N*-(2-chloroethyl)-*N*-(1*H*-imidazol-4-ylmethyl)amine dihydrochloride



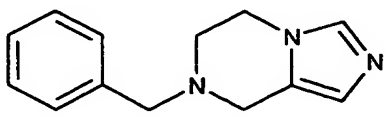
Thionyl chloride (11.35mL, 155.6mmol) was added to a solution of the alcohol from preparation 77 (9.0g, 38.9mmol) in dichloromethane (200mL) over 20 minutes. The solution was then stirred under reflux for 3 hours, and allowed to cool. The mixture was concentrated under reduced pressure and azeotroped with acetonitrile (2x) and dried *in vacuo*, to afford the title compound as a solid, 11.14g.

^{1}H-nmr (CD_3OD, 400MHz) δ: 3.24 (m, 2H), 3.78 (m, 2H), 4.15 (s, 2H), 4.25 (s, 2H), 7.40 (m, 3H), 7.46 (m, 2H), 7.64 (s, 1H), 8.88 (s, 1H).

LRMS : m/z (ES^+) 250 $[MH^+]$

Preparation 79

7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine



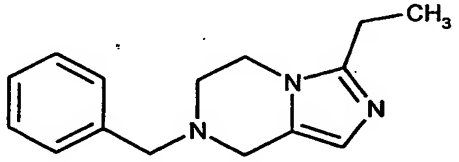
Triethylamine (19.55mL, 140mmol) was added to a solution of the chloride from preparation 78 (11.12g, 38.9mmol) in acetonitrile (150mL) over 20 minutes, and the reaction heated under reflux for 6 hours. The cooled mixture was filtered, and the filtrate concentrated under reduced pressure. The residual oil was partitioned between dichloromethane (300mL) and saturated sodium bicarbonate solution (150mL) and the phases separated. The aqueous layer was extracted with further dichloromethane (2x300mL), and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound as an orange solid, 3.62g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.84 (t, 2H), 3.67 (s, 2H), 3.70 (s, 2H) 4.02 (t, 2H), 6.73 (s, 1H), 7.25-7.35 (m, 6H).

LRMS : m/z (ES^+) 214 [MH^+]

Preparation 80

7-Benzyl-3-ethyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine



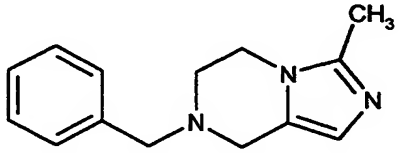
n-Butyllithium (3.3mL, 1.6M in hexanes, 5.28mmol) was added dropwise to a cooled (-78°C) solution of the compound from preparation 79 (1.0g, 4.69mmol) in tetrahydrofuran (10mL), so as to maintain the temperature below -70°C, and the solution then allowed to warm to 0°C over 30 minutes. Ethyl iodide (1.22mL, 15.0mmol) was added, and the mixture stirred at 0°C for 45 minutes. The reaction was allowed to warm to room temperature, then partitioned between ethyl acetate (30mL) and saturated sodium bicarbonate solution (6mL). The phases were separated, the aqueous layer extracted with further ethyl acetate, and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (99:1 to 90:10) to afford the title compound as an orange oil, 552mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.30 (t, 3H), 2.62 (q, 2H), 2.84 (t, 2H), 3.63 (s, 2H), 3.68 (s, 2H), 3.85 (t, 2H), 6.62 (s, 1H), 7.24-7.34 (m, 5H).

LRMS : m/z (ES^+) 242 [MH^+]

Preparation 81

7-Benzyl-3-m thyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine



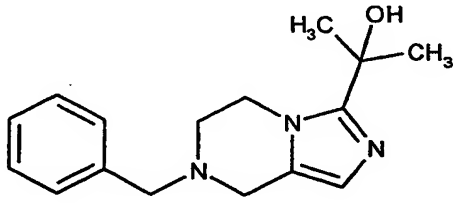
The title compound was obtained as an orange oil in 89% yield from the compound from preparation 79 and methyl iodide, following the procedure described in preparation 80.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.30 (s, 3H), 2.84 (t, 2H), 3.62 (s, 2H), 3.68 (s, 2H), 3.83 (t, 2H), 6.59 (s, 1H), 7.25-7.34 (m, 5H).

LRMS : m/z (ES^+) 228 [MH^+]

Preparation 82

2-(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-yl)-2-propanol



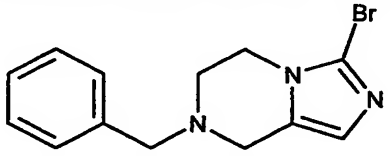
n-Butyllithium (6.21mL, 1.6M in hexanes, 9.94mmol) was added dropwise to a cooled (-78°C) solution of the compound from preparation 79 (2.0g, 9.38mmol) in tetrahydrofuran (20mL), so as to maintain the temperature below -70°C, and the solution then allowed to warm to 0°C over 30 minutes. Acetone (2.06mL, 28.13mmol) was added, and the mixture stirred at 0°C for 45 minutes. The reaction was allowed to warm to room temperature, then quenched by the addition of water (10mL), then neutralised using 2N hydrochloric acid. The mixture was extracted with ethyl acetate (3x50mL), and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (99:1 to 94:6) to afford the title compound as a solid, 1.21g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.63 (s, 6H), 2.80 (t, 2H), 3.63 (s, 2H), 3.67 (s, 2H), 4.23 (t, 2H), 6.60 (s, 1H), 7.25-7.39 (m, 5H).

LRMS : m/z (ES^+) 272 [MH^+]

Preparation 83

7-Benzyl-3-bromo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine



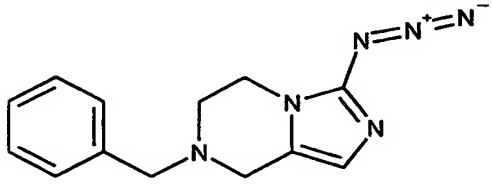
n-Butyllithium (2.2mL, 2.5M in hexane, 5.5mmol) was added dropwise to a cooled (-78°C) solution of the compound from preparation 79 (1.07g, 5mmol) in tetrahydrofuran (20mL), and the solution stirred for 15 minutes. Bromine (880mg, 5.5mmol) was then added dropwise, the reaction stirred for a further 15 minutes, then poured into water. The mixture was extracted with dichloromethane (3x50mL), the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography using an elution gradient of dichloromethane:methanol (100:0 to 95:5), then repeated using dichloromethane:ethyl acetate (100:0 to 60:40), to afford the titl compound as a pale yellow crystalline solid, 979mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.86 (t, 2H), 3.62 (s, 2H), 3.69 (s, 2H), 3.86 (t, 2H), 6.71 (s, 1H), 7.25-7.34 (m, 5H).

LRMS : m/z (ES^+) 314, 316 [MNa^+]

Preparation 84

3-Azido-7-benzyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine



n-Butyllithium (1.23mL, 2.5M in hexanes, 3.09mmol) was added to a cooled (-78°C) solution of the compound from preparation 79 (548mg, 2.57mmol) in tetrahydrofuran (10mL), and the mixture stirred for 10 minutes. p-Toluenesulphonyl azide (WO 9824759) (609mg, 3.09mmol) was added, the

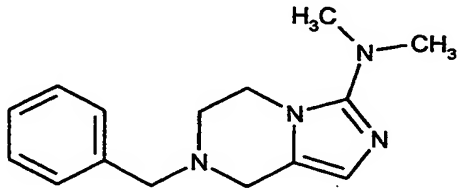
reaction stirred for a further 10 minutes, and then saturated sodium bicarbonate solution (4mL) added. The mixture was warmed to room temperature, diluted with brine, and extracted with dichloromethane (2x60mL). The combined organic solutions were dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:ethyl acetate (100:0 to 60:40) to afford the title compound as a yellow-orange oil, 154mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.79 (t, 2H), 3.58 (s, 2H), 3.66 (s, 2H), 3.70 (t, 2H), 6.56 (s, 1H), 7.25-7.36 (m, 5H).

LRMS : m/z (ES^+) 277 [MNa^+]

Preparation 85

N-(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-yl)-*N*,*N*-dimethylamine



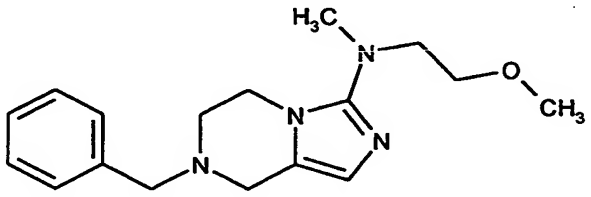
A solution of the bromide from preparation 83 (950mg, 3.25mmol) in ethanolic dimethylamine (33%, 12mL) was heated at 140°C in a sealed vessel for 4 days. The cooled mixture was poured into water, and extracted with dichloromethane (3x50mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5) and repeated using ethyl acetate:methanol (100:0 to 95:5) to afford the titl compound as an orange oil, 172mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.75 (s, 6H), 2.79 (t, 2H), 3.60 (s, 2H), 3.67 (s, 2H), 3.80 (t, 2H), 6.44 (s, 1H), 7.25-7.38 (m, H).

LRMS : m/z (ES^+) 257 [MH^+]

Preparation 86

7-Benzyl-*N*-(2-methoxyethyl)-*N*-methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine



A solution of the bromide from preparation 83 (52mg, 0.18mmol) in N-(2-methoxyethyl)methylamine (3mL) was heated at 140°C for 18 hours in a sealed vessel. The reaction was heated to 185°C for a further 5 hours, then cooled and partitioned between 0.1N sodium hydroxide solution and dichloromethane. The layers were separated, the aqueous phase extracted with further dichloromethane (2x50mL), and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate:methanol:0.88 ammonia (100:0:0 to 93:7:0.7) to afford the title compound as a yellow oil, 75mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.76 (m, 5H), 3.18 (t, 2H), 3.32 (s, 3H), 3.48 (t, 2H), 3.59 (s, 2H), 3.66 (s, 2H), 3.82 (t, 2H), 6.46 (s, 1H), 7.25-7.36 (m, 5H).

LRMS : m/z (ES^+) 323 [MNa^+]

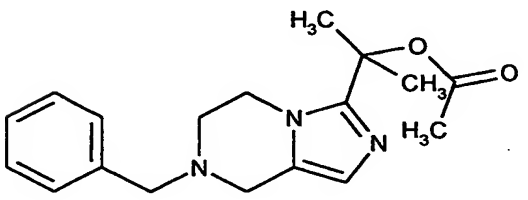
Preparation 87

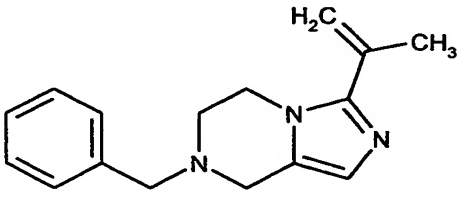
1-(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-yl)-1-methylethyl acetate

and

Preparation 88

7-Benzyl-3-isopropenyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine





Acetic anhydride (541µl, 5.74mmol) was added dropwise to a solution of the alcohol from preparation 82 (1.25g, 4.59mmol) in pyridine (20mL), containing 4-

dimethylaminopyridine (70mg, 0.57mmol). The solution was stirred at room temperature for 72 hours then evaporated under reduced pressure. The residual orange oil was partitioned between ethyl acetate (100mL) and 10% sodium bicarbonate solution (50mL), and the layers separated. The organic phase was washed with water (2x50mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 94:6) to afford the title compound as an orange oil, 471mg.

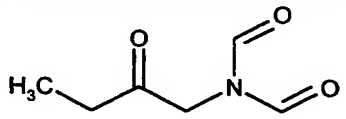
^{1}H-nmr ($CDCl_3$, 400MHz) (2:3 mixture of compounds) δ: 1.84 (s, 6H), *2.02 (s, 3H),* 2.19 (s, 3H), 2.80 (t, 2H), *2.80 (t, 2H), 3.65 (2xs, 4H),* 3.70 (2xs, 4H), 4.04 (m, 2H), *4.04 (m, 2H), 5.29 (s, 2H), 6.64 (s, 1H),* 6.77 (s, 1H), 7.27-7.37 (m, 5H), *7.27-7.37 (m, 5H).*

LRMS : m/z (ES^+) 336 [MNa^+] (preparation 87)

LRMS : m/z (ES^+) 254 [MH^+] (preparation 88)

Preparation 89

Formyl(2-oxobutyl)formamide

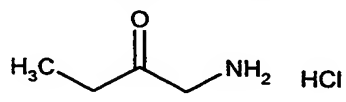


A mixture of bromobutan-2-one (10g, 66mmol), and sodium diformylamide (6.8g, 72mmol) in acetonitrile (50mL) was stirred at room temperature for 3 hours, th n warmed to 35°C for 2 hours. The mixture was stirred for a further 48 hours at room temperature, then filtered, washing through with additional acetonitrile (50mL). The filtrate was evaporated under reduced pressure to afford the title compound as a clear oil, 9.1g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ : 1.10 (t, 3H), 2.50 (q, 2H), 4.42 (s, 2H), 8.90 (bs, 2H).

Preparation 90

1-Amino-2-butanone hydrochloride



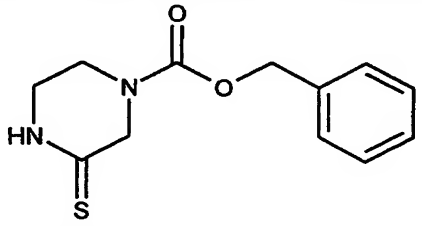
A solution of the compound from preparation 89 (9.1g, 63.6mmol) in ethanolic hydrochloric acid (5%, 175mL) was stirred at room temperature for 48 hours. The reaction was then evaporated under reduced pressure to afford the title compound as a tan-coloured solid, 6.3g.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.96 (t, 3H), 2.50 (q, 2H), 3.84 (bs, 2H), 8.38 (bs, 3H).

LRMS : m/z (ES$^+$) 175 [2M+H]$^+$

Preparation 91

Benzyl 3-thioxo-1-piperazinecarboxylate



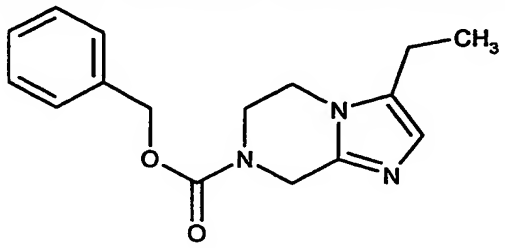
Lawesson's reagent (10.1g, 20mmol) was added to a solution of benzyl 3-oxo-1-piperazinecarboxylate (10g, 43mmol) in tetrahydrofuran (110mL), and the reaction heated under reflux for 4 hours. The cooled mixture was concentrated und r reduced pressure and the residue partitioned between 1N sodium hydroxide solution (150mL) and ethyl acetate (250mL), and the layers separated. The organic extract was washed with 1N sodium hydroxide solution (2x100mL), th n brine (100mL), and the combined aqueous solutions extracted with ethyl acetate (200mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound as a tan-coloured solid, 6.7g.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 3.24-3.34 (m, 2H), 3.58 (m, 2H), 4.36 (s, 2H), 5.10 (s, 2H), 7.30-7.40 (m, 5H).

LRMS : m/z (ES$^+$) 273 [MNa$^+$]

Preparation 92

Benzyl 3-ethyl-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate



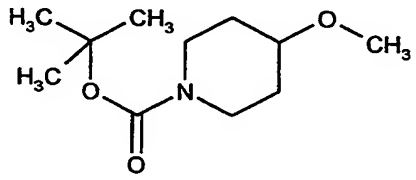
Methyl iodide (2.18mL, 35mmol) was added to a solution of the compound from preparation 91 (1g, 3.5mmol) in tetrahydrofuran (15mL), and the reaction stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure, the residue re-dissolved in tetrahydrofuran (15mL), diisopropylethylamine (1mL) and the compound from preparation 90 (500mg, 4mmol) added, and the solution stirred at room temperature for 18 hours, followed by a further 2 hours under reflux. Acetic acid (15mL) was added, the mixture concentrated under reduced pressure to a volume of about 15mL, then heated under reflux for 1 hour. The reaction was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using dichloromethane:methanol (95:5) as eluant to afford the title compound as a pale orange solid, 620mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 1.14 (t, 3H), 3.10 (q, 2H), 3.60 (m, 2H), 3.82 (m, 2H), 4.60 (bs, 2H), 5.12 (s, 2H), 6.64 (s, 1H), 7.36 (m, 5H).

LRMS : m/z (ES$^+$) 286 $[MH]^+$

Preparation 93

tert-Butyl 4-methoxy-1-piperidinecarboxylate



Sodium hydride (1.19g, 60% in mineral oil, 29.7mmol) was added portionwise to a cooled (10°C) solution of *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (Bioorg. Med. Chem. Lett. 10;24;2000;2815) in tetrahydrofuran (80mL), and the

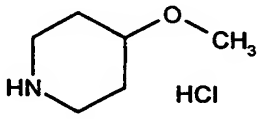
suspension stirred at room temperature for 1 hour. Iodomethane (1.85mL, 29.7mmol) was added, and the reaction stirred at 50°C for 20 hours. The mixture was diluted with water (50mL), extracted with ethyl acetate (2x150mL) and the combined organic extracts washed with saturated sodium bicarbonate solution (50mL), dried ($MgSO_4$) and evaporated under reduced pressure, to afford the title compound as a golden oil, 5.24g.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.47 (s, 9H), 1.50 (m, 2H), 1.80 (m, 2H), 3.08 (m, 2H), 3.34 (m, 4H), 3.75 (m, 2H).

LRMS : m/z (ES^+) 238 [MNa^+]

Preparation 94

4-Methoxypiperidine hydrochloride



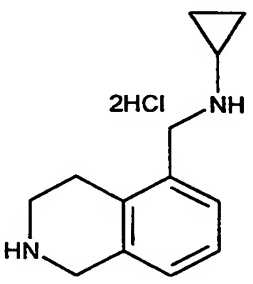
Hydrogen chloride was bubbled through an ice-cooled solution of the compound from preparation 93 (5.2g, 24.2mmol) in dichloromethane (100mL), and the reaction stirred for 1.5 hours. The solution was purged with nitrogen, then evaporated under reduced pressure to afford the title compound as an off-white solid, 3.67g.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 1.87 (m, 2H), 1.99 (m, 2H), 3.10 (m, 2H), 3.28 (m, 2H), 3.36 (s, 3H), 3.54 (m, 1H).

LRMS : m/z (ES^+) 231 [$2MH^+$]

Preparation 95

N-(1,2,3,4-Tetrahydro-5-isoquinolinylmethyl)cyclopropanamine dihydrochlorid



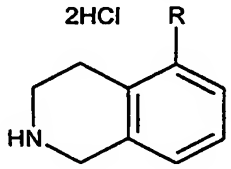
Hydrogen chloride was bubbled through an ice-cooled solution of the protected amine from preparation 29 (1.17g, 3.87mmol) in dichloromethane (35mL), for 20 minutes. The reaction was then stirred for a further 30 minutes at room temperature and evaporated under reduced pressure to afford the title compound as a white solid, 1.15g.

^{1}Hnmr (DMSOd_6, 400MHz) δ: 0.83 (m, 2H), 0.95 (m, 2H), 2.67 (m, 1H), 3.10 (t, 2H), 3.34 (m, 2H), 4.17 (s, 2H), 4.26 (s, 2H), 7.26 (m, 2H), 7.48 (d, 1H), 9.60 (bs, 4H).

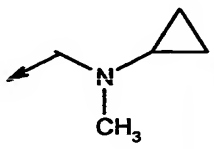
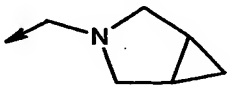
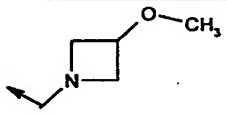
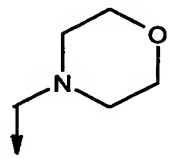
LRMS : m/z (ES$^+$) 203 [MH$^+$]

Preparations 96 to 99

The following compounds of general structure:



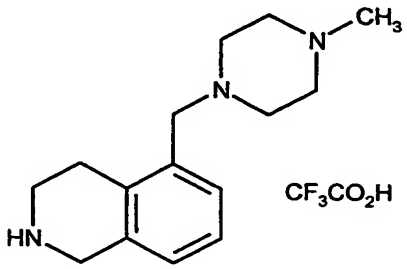
were prepared from the corresponding protected amines, following the procedure described in preparation 95.

Prep no	R	Form	Data
96		White solid	^{1}Hnmr (DMSOd_6, 400MHz) (rotamers) δ: 0.70 (m, 4H), 1.15 (m, 1H), 2.67 (2xs, 3H), 2.90 (m, 1H), 3.33 (m, 2H), 4.20 (s, 2H), 4.40 (2xs, 2H), 7.30 (m, 2H), 7.60 (m, 1H), 9.63 (bs, 2H), 10.76 (bs, 1H). LRMS : m/z (ES$^+$) 217 [MH$^+$]
97		White foam	^{1}Hnmr (DMSOd_6, 400MHz) δ: 0.59 (m, 1H), 1.34 (m, 1H), 1.72 (m, 2H), 3.18 (m, 2H), 3.36 (m, 6H), 4.21 (s, 2H), 4.34 (d, 2H), 7.24 (m, 2H), 7.73 (m, 1H), 9.58 (bs, 2H), 10.95 (bs, 1H). LRMS : m/z (ES$^+$) 229 [MH$^+$]
98		White foam	^{1}Hnmr (DMSOd_6, 400MHz) δ: 3.01-3.40 (m, 7H), 3.90 (bs, 1H), 4.01 (bs, 1H), 4.22 (m, 6H), 4.40 (s, 2H), 7.28 (m, 2H), 7.43 (m, 1H), 9.40-9.56 (m, 2H). LRMS : m/z (ES$^+$) 234 [MH$^+$]
99		White solid	^{1}Hnmr (DMSOd_6, 400MHz) δ: 3.20 (m, 4H), 3.37 (m, 2H), 3.62 (m, 2H), 3.90 (m, 4H), 4.22 (m, 2H), 4.32 (s, 2H), 7.30 (m, 2H), 7.62 (m, 1H), 9.58 (bs, 2H), 11.40 (bs, 1H). LRMS : m/z (ES$^+$) 233 [MH$^+$]

(a)-isolated as the trihydrochloride salt

Preparation 100

5-[(4-Methyl-1-piperazinyl)methyl]-1,2,3,4-t trahydroisoquinolin trifluoroacetate



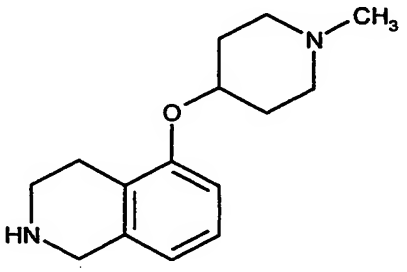
Trifluoroacetic acid (1mL) was added to an ice-cooled solution of the protected amine from preparation 44 (200mg, 0.58mmol) in dichloromethane (3mL), and the reaction stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure and the residue azeotroped with toluene (2x) and dichloromethane (3x) to afford the title compound.

^{1}Hnmr (DMSOd_6, 400MHz) δ: 2.79 (s, 3H), 2.81-3.04 (m, 6H), 3.38 (m, 4H), 3.58 (m, 2H), 4.28 (t, 2H), 7.16 (m, 1H), 7.24 (m, 2H), 9.03 (bs, 2H).

LRMS : m/z (ES$^+$) 246 [MH$^+$]

Preparation 101

5-[(1-Methyl-4-piperidinyl)oxy]-1,2,3,4-tetrahydroisoquinoline



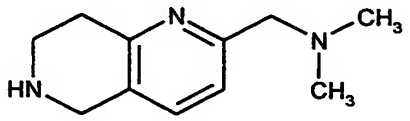
Trifluoroacetic acid (5mL) was added dropwise to a solution of the protect d amine from preparation 47 (420mg, 1.21mmol) in dichloromethane (5mL), and th solution stirred at room temperature for 4 hours. The solution was concentrat d under reduced pressure and azeotroped twice with toluene. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichlorom thane:methanol:0.88 ammonia (97:3:0.2 to 90:10:1) to afford the title compound as a colourless oil, 198mg.

^{1}Hnmr ($CDCl_3$, 400MHz) δ: 1.73 (m, 1H), 1.87 (m, 2H), 1.98 (m, 2H), 2.30 (s, 3H), 2.33 (m, 2H), 2.62 (m, 2H), 2.68 (t, 2H), 3.13 (t, 2H), 3.97 (s, 2H), 4.35 (m, 1H), 6.61 (d, 1H), 6.66 (d, 1H), 7.07 (dd, 1H).

LRMS : m/z (ES^+) 247 [MH^+]

Preparation 102

N,N-Dimethyl(5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)methanamine



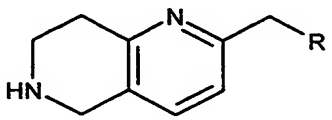
A solution of the protected naphthyridine from preparation 48 (600mg, 2.13mmol) in methanol (60mL) was purged with argon, then heated to reflux. Immediately this was achieved, 10% palladium on charcoal (600mg) and ammonium formate (268mg, 4.26mmol) were added, and the mixture stirred under reflux for 3 minutes. The reaction vessel was then immersed in cold water, and the cooled mixture then filtered through Arbocel®, washing through with ethanol. The filtrate was evaporated under reduced pressure and the residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0.2 to 90:10:1) to afford the title compound as a colourless oil, 259mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.28 (s, 6H), 2.96 (t, 2H), 3.21 (t, 2H), 3.56 (s, 2H), 3.98 (s, 2H), 7.18 (d, 1H), 7.25 (d, 1H).

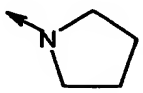
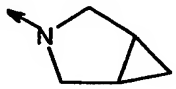
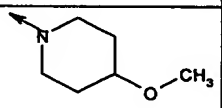
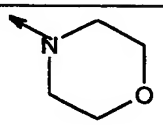
LRMS : m/z (ES^+) 214 [MNa^+]

Preparations 103 to 106

The following compounds of general structure:



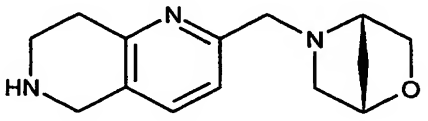
were prepared from the corresponding protected naphthryidines, following a similar procedure to that described in preparation 102.

Prep	R	Yield/ Form	Data
103		55 colour-less oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.78 (m, 4H), 2.58 (m, 4H), 2.94 (t, 2H), 3.21 (t, 2H), 3.73 (s, 2H), 3.98 (s, 2H), 7.17 (d, 1H), 7.25 (d, 1H). LRMS : m/z (ES^+) 218 [MH^+]
104 (a)			^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.30 (m, 1H), 0.62 (m, 1H), 1.34 (m, 2H), 2.37 (m, 2H), 2.75 (m, 2H), 2.85 (m, 2H), 3.04 (m, 2H), 3.59 (s, 2H), 3.83 (s, 2H), 7.08 (d, 1H), 7.37 (d, 1H), 8.25 (s, 1H). LRMS : m/z (ES^+) 230 [MH^+]
105		88 colour-less oil	^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 1.40 (m, 2H), 1.80 (m, 2H), 2.16 (m, 2H), 2.64 (m, 2H), 2.70 (m, 2H), 2.98 (m, 2H), 3.18 (s, 3H), 3.20 (m, 1H), 3.44 (s, 2H), 3.80 (s, 2H), 7.12 (d, 1H), 7.38 (d, 1H). LRMS : m/z (ES^+) 262 [MH^+]
106		72 yellow oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.55 (m, 4H), 2.93 (t, 2H), 3.21 (t, 2H), 3.60 (s, 2H), 3.71 (m, 4H), 3.98 (s, 2H), 7.19 (d, 1H), 7.26 (d, 1H). LRMS : m/z (ES^+) 234 [MH^+]

(a)-compound isolated without column chromatography

Preparation 107

(1*S*,4*S*)-5-(5,6,7,8-Tetrahydro[1,6]naphthyridin-2-ylmethyl)-2-oxa-5-azabicyclo[2.2.1]heptane



1-Chloroethyl chloroformate (79mg, 0.55mmol) was added to a solution of the compound from preparation 52 (168mg, 0.5mmol) in acetonitrile (5mL), and the

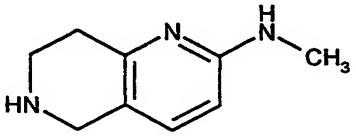
reaction warmed to 50°C, and th stirred for 30 minutes. The cooled mixture was concentrated under reduced pressure and the residu re-dissolved in methanol (5mL), and the solution stirred under reflux for 45 minut s. The cooled solution was purified directly by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1) to afford the title compound as a pale orange oil, 66mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.80 (m, 1H), 1.99 (m, 1H), 2.71 (m, 1H), 3.01 (m, 1H), 3.04 (t, 2H), 3.32 (t, 2H), 3.59 (m, 1H), 3.67 (m, 1H), 3.94 (q, 2H), 4.11 (s, 2H), 4.16 (m, 1H), 4.44 (m, 1H), 7.35 (s, 2H).

LRMS : m/z (APCI$^+$) 246 [MH$^+$]

Preparation 108

N-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-amine



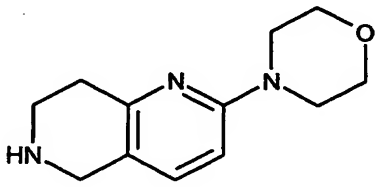
A mixture of the protected naphthyridine from preparation 54 (1.28g, 5.05mmol) and 10% palladium on charcoal (130mg) in 1N hydrochloric acid (10.5mL) was hydrogenated at 30°C and 30 psi for 17 hours. The reaction mixture was filtered through Arbocel®, washing through with water and ethanol. The combined filtrate was evaporated under reduced pressure and the residual solid was suspended in a warm solution of water (20mL) and 1N hydrochloric acid (4mL) and the mixture filtered through Arbocel®. The filtrate was concentrated under reduced pressure and azeotroped with ethanol, ethyl acetate and diethyl ether. The product was recrystallised from methanol and ethyl acetate to afford the title compound as a solid, 300mg.

^{1}H-nmr (D_2O, 400MHz) δ: 2.95 (s, 3H), 3.15 (m, 2H), 3.57 (m, 2H), 4.20 (s, 2H), 6.84 (d, 1H), 7.59 (d, 1H).

LRMS : m/z (ES$^+$) 164 [MH$^+$]

Preparation 109

2-(4-Morpholinyl)-5,6,7,8-t trahydro[1,6]naphthyridin



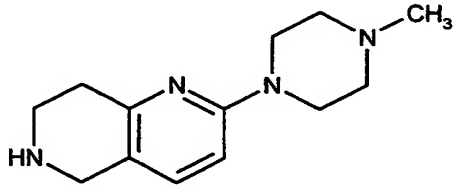
Ammonium formate (1.02g, 16mmol), followed by 10% palladium on charcoal (1g) were added to a solution of the protected naphthyridine from preparation 55 (1g, 3.2mmol) in methanol (20mL), and the reaction heated under reflux for 1.5 hours. The cooled mixture was filtered through Arbocel®, washing through with dichloromethane and methanol, and the filtrate evaporated under reduced pressure. The product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0 to 94:5:1) to afford the title compound, 425mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.79 (t, 2H), 3.17 (t, 2H), 3.44 (m, 4H), 3.79 (m, 4H), 3.91 (s, 2H), 6.42 (d, 1H), 7.15 (d, 1H).

LRMS : m/z (ES^+) 220 [MH^+]

Preparation 110

2-(4-Methyl-1-piperazinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine

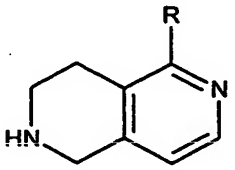


The title compound was obtained in 21% yield from the protected naphthyridine from preparation 56, following the procedure described in preparation 109.

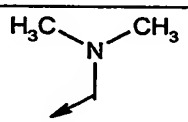
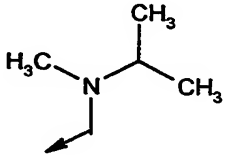
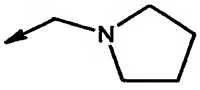
^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.32 (s, 3H), 2.49 (m, 4H), 2.72 (t, 2H), 3.15 (t, 2H), 3.51 (m, 4H), 3.83 (s, 2H), 6.43 (d, 1H), 7.10 (d, 1H).

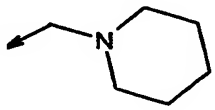
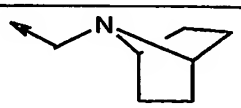
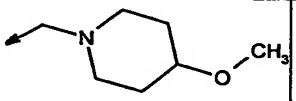
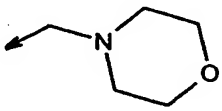
LRMS : m/z (ES^+) 233 [MH^+]

Preparations 111 to 118



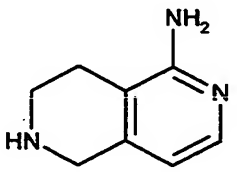
Ammonium formate (5-25eq) was added to a solution of the appropriate protected amines (1eq) in methanol. 10% Palladium on charcoal (1:1 w/w eq) was added portionwise, and the mixture stirred under reflux for 0.5 to 4 hours. The cooled mixture was filtered through Arbocel®, washing through with dichloromethane or dichloromethane:methanol (95:5) and the combined filtrates were evaporated under reduced pressure. The crude products were purified by column chromatography on silica gel using elution gradients of dichloromethane:methanol:0.88 ammonia, to afford the title compounds.

Prep	R	Yield/ Form	Data
111		41 clear oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.22 (s, 6H), 2.84 (t, 2H), 3.18 (t, 2H), 3.52 (s, 2H), 3.98 (s, 2H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 192 [MH^+]
112		52 colour-less oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.06 (d, 6H), 2.12 (s, 3H), 2.89 (m, 3H), 3.16 (t, 2H), 3.63 (s, 2H), 3.98 (s, 2H), 6.81 (d, 1H), 8.25 (d, 1H). LRMS : m/z (ES^+) 220 [MH^+]
113		69	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.78 (m, 4H), 2.58 (m, 4H), 2.86 (m, 2H), 3.18 (m, 2H), 3.70 (s, 2H), 3.97 (s, 2H), 6.81 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 218 [MH^+]

Prep	R	Yield/ Form	Data
114		65 yellow gum	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.41 (m, 2H), 1.53 (m, 4H), 2.41 (m, 4H), 2.90 (t, 2H), 3.16 (t, 2H), 3.54 (s, 2H), 3.98 (s, 2H), 6.81 (d, 1H), 8.25 (d, 1H). LRMS : m/z (ES^+) 254 [MNa^+]
115		24 colour-less oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.25 (m, 4H), 1.78 (m, 4H), 2.92 (t, 2H), 3.16 (t, 2H), 2.23 (m, 2H), 3.59 (s, 2H), 3.98 (s, 2H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 244 [MH^+]
116		84 orange oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.58 (m, 4H), 1.85 (m, 2H), 2.20 (m, 2H), 2.75 (m, 2H), 2.90 (m, 2H), 3.18 (m, 4H), 3.59 (s, 2H), 3.98 (s, 2H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 262 [MH^+]
117		75 colour-less oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.48 (m, 4H), 2.88 (t, 2H), 3.18 (t, 2H), 3.60 (s, 2H), 3.65 (m, 4H), 3.98 (s, 2H), 6.81 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 234 [MH^+]
118		85 oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.90 (d, 1H), 2.67 (d, 1H), 2.88 (m, 4H), 3.18 (m, 2H), 3.41 (s, 1H), 3.61 (d, 1H), 3.82 (m, 2H), 3.98 (s, 2H), 4.07 (d, 1H), 4.37 (s, 1H), 6.82 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 468 [MNa^+]

Preparation 119

5,6,7,8-Tetrahydro[2,6]naphthyridin-1-amine



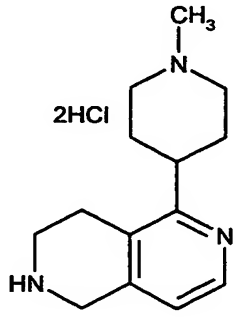
A mixture of the protected amine from preparation 68 (234mg, 0.71mol), ammonium formate (2.34g, 37mmol) and 10% palladium on charcoal (234mg) in methanol (10mL) was heated under reflux for 2 hours. Additional ammonium formate (2.34g, 37mmol) and 10% palladium on charcoal (234mg) were added, and the mixture heated for a further 4 hours. The cooled mixture was diluted with dichloromethane (50mL), filtered through Arbocel® and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1) as eluant to afford the title compound, as a solid, 21mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.40 (t, 2H), 3.20 (t, 2H), 3.88 (s, 2H), 4.34 (bs, 2H), 6.38 (d, 1H), 7.82 (d, 1H).

LRMS : m/z (ES^+) 150 [MH^+]

Preparation 120

5-(1-Methyl-4-piperidinyl)-1,2,3,4-tetrahydro[2,6]naphthyridine dihydrochlorid



Formic acid (150μl, 3.92mmol) followed by 10% palladium on charcoal (150mg) were added to a solution of the protected naphthyridine from preparation 67 (630mg, 1.96mmol) in methanol (10mL), and the mixture heated under reflux for 4 hours. Additional 10% palladium on charcoal (350mg) and formic acid (150μl) were added, and the mixture stirred under reflux for a further 18 hours. The cooled

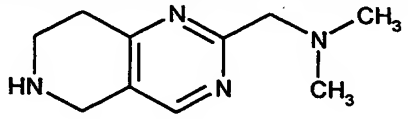
reaction mixture was filtered through Arbocel®, washing through with methanol (300mL), and the combined filtrates evaporated under reduced pressure. The residual oil was dissolved in 1N hydrochloric acid (6mL), and th solution stirred under reflux for 1 hour. The cooled solution was concentrated under reduced pressure, azeotroped with methanol and dichloromethane to afford the title compound as a pale yellow foam, 590mg.

^{1}H-nmr (CD_3OD, 40MHz) δ: 2.18 (m, 2H), 2.26 (m, 2H), 2.95 (s, 3H), 3.30 (m, 4H), 3.50 (m, 1H), 3.62 (m, 4H), 4.58 (s, 2H), 7.56 (d, 1H), 8.57 (d, 1H).

LRMS : m/z (ES^+) 232 [MH^+]

Preparation 121

N,N-Dimethyl(5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-yl)methanamine



2HCl

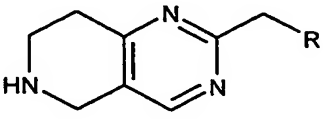
Hydrogen chloride gas was bubbled through an ice-cooled solution of the protected amine from preparation 71 (267mg, 0.91mmol) in dichloromethane (15mL), for 10 minutes, and the reaction then stirred for a further 20 minutes at room temperature. The solution was evaporated under reduced pressure, dissolved in methanol (5mL), and diluted with ethyl acetate (40mL). The solution was evaporated under reduced pressure to afford the title compound as a buff-coloured solid.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 2.96 (s, 6H), 3,17 (t, 2H), 3.45 (t, 2H), 4.37 (s, 2H), 4.60 (s, 2H), 8.79 (s, 1H), 10.00-10.20 (bs, 3H).

LRMS : m/z (ES^+) 193 [MH^+]

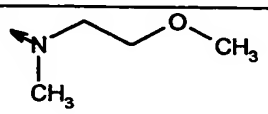
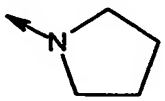
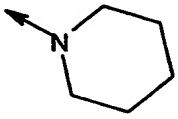
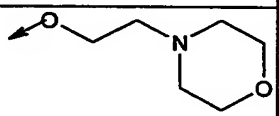
Preparations 122 to 125

The following compounds of general structure:



2HCl

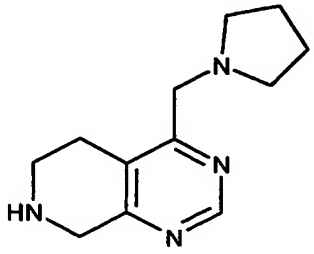
were prepared from the appropriate protected amines following a similar procedure to that described in preparation 121.

Prep	R	Form	Data
122		Brown solid	^{1}H-nmr (DMSOd_6, 400MHz) δ: 2.90 (s, 3H), 3.17 (t, 2H), 3.25 (s, 3H), 3.37-3.60 (m, 4H), 3.72 (t, 2H), 4.36 (s, 2H), 4.60 (bd, 2H), 8.78 (s, 1H), 10.00 (bs, 2H), 10.20 (bs, 1H). LRMS : m/z (ES$^+$) 237 [MH$^+$]
123 [(a)]		Yellow foam	^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.98 (m, 4H), 3.23 (m, 4H), 3.45 (t, 2H), 3.65 (m, 2H), 4,30 (s, 2H), 4.65 (s, 2H), 8.74 (s, 1H), 9.50 (bs, 2H). LRMS : m/z (ES$^+$) 219 [MH$^+$]
124		Tan solid	^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.60-1.80 (m, 6H), 3.15 (m, 2H), 3.17 (t, 2H), 3.45 (m, 4H), 4.38 (s, 2H), 4.58 (s, 2H), 8.79 (s, 1H), 9.96-10.17 (m, 3H). LRMS : m/z (ES$^+$) 233 [MH$^+$]
125		95 solid	^{1}H-nmr (DMSOd_6+dropTFAd, 400MHz) δ: 3.10 (m, 4H), 3.36 (m, 2H), 3.52 (m, 2H), 3.81 (m, 4H), 3.94 (m, 4H), 4.30 (m, 2H), 4.69 (s, 2H), 8.67 (s, 1H), 9.85 (bs, 2H). LRMS : m/z (ES$^+$) 279 [MH$^+$]

(a)-compound azeotroped with dichloromethane

Preparation 126

4-(1-Pyrrolidinylm thyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine



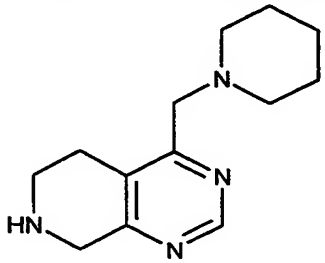
A solution of the protected amine from preparation 69 (395mg, 1.28mmol) in methanol (25mL), was allowed to stand under a nitrogen atmosphere. 10% Palladium on charcoal (395mg), followed by ammonium formate (1.0g, 15.9mmol) was added, and the mixture stirred vigorously under reflux for 30 minutes. The cooled mixture was diluted with dichloromethane (100mL), filtered through Arbocel® and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography using dichloromethane:methanol:0.88 ammonia (97:3:1) as eluant to afford the title compound as a colourless oil, that crystallised on standing, 174mg.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.78 (m, 4H), 2.57 (m, 4H), 2,85 (t, 2H), 3,15 (t, 2H), 3.68 (s, 2H), 4.04 (s, 2H), 8.89 (s, 1H).

LRMS : m/z (ES^+) 219 [MH^+]

Preparation 127

4-(1-Piperidinylmethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine



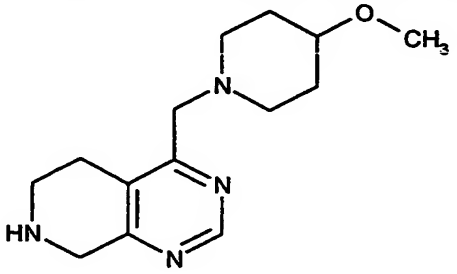
The title compound was obtained as an orange oil in 43% yield from the protected amine from preparation 72, following the procedure described in preparation 126.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.42 (m, 2H), 1.55 (m, 4H), 2.41 (m, 4H), 2.89 (t, 2H), 3.14 (t, 2H), 3.50 (s, 2H), 4.05 (s, 2H), 8.87 (s, 1H).

LRMS : m/z (ES^+) 233 [MH^+]

Preparation 128

4-[(4-Methoxy-1-piperidinyl)methyl]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine



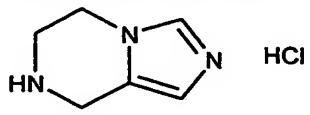
The title compound was obtained in 42% yield as a yellow oil, from the protected amine from preparation 76, following a similar procedure to that described in preparation 126.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 1.56 (m, 2H), 1.84 (m, 2H), 2.24 (m, 2H), 2.73 (m, 2H), 2.88 (t, 2H), 3.15 (t, 2H), 3.20 (m, 1H), 3.32 (s, 3H), 3.53 (s, 2H), 4.05 (s, 2H), 8.87 (s, 1H).

LRMS : m/z (ES^+) 263 [MH^+]

Preparation 129

5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyrazine hydrochloride



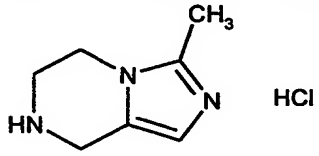
10% Palladium on charcoal (100mg) was added portionwise to a solution of the protected amine from preparation 79 (900mg, 4.22mmol) in methanol (10mL), followed by formic acid (0.25mL), and the reaction stirred under reflux for 5 hours. The cooled mixture was diluted with water (5mL), filtered through Arbocel®, and washed through with methanol (200mL). The filtrate was concentrated under reduced pressure and azeotroped with dichloromethane. The residual oil was dissolved in 1N hydrochloric acid (10mL), and the solution stirred under reflux for 2 hours. The cooled solution was evaporated under reduced pressure and the resulting solid recrystallised from methanol to afford the title compound as a white solid, 500mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 3.58 (t, 2H), 4.40 (s, 2H), 4.50 (t, 2H), 7.56 (s, 1H), 9.10 (s, 1H).

LRMS : m/z (ES^+) 125 [MH^+]

Preparation 130

3-Methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine hydrochloride



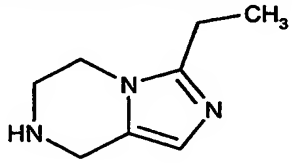
Ammonium formate (3.33g, 52.8mmol) and 10% palladium on charcoal (800mg) were added to a solution of the protected amine from preparation 81 (800mg, 3.52mmol) in methanol (10mL) and 2N hydrochloric acid (0.5mL), and the reaction heated under reflux for 25 hours. The cooled mixture was diluted with water (5mL), then filtered through Arbocel®. The filtrate was evaporated under reduced pressure, and the residual solid purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 90:10:1) to give a solid. This was dissolved in 2N hydrochloric acid (10mL), the solution heated under reflux for 2 hours, then cooled and evaporated under reduced pressure, azeotroping with dichloromethane, to afford the title compound as a white solid, 536mg.

^{1}H-nmr (CD_3OD, 400MHz) δ: 2.66 (s, 3H), 3.81 (t, 2H), 4.44 (t, 2H), 4.57 (s, 2H), 7.46 (s, 1H).

LRMS : m/z (ES^+) 138 [MH^+]

Preparation 131

3-Ethyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine



Ammonium formate (2.12g, 33.6mmol) and 10% palladium on charcoal (550mg) were added to a solution of the protected amine from preparation 80 (541mg, 2.24mmol) in methanol (15mL) and 2N hydrochloric acid (0.5mL), and the reaction heated under reflux for 26 hours. The cooled mixture was diluted with water (5mL), then filtered through Arbocel®, washing through with dichloromethane:methanol solution (1:1, 300mL). The filtrate was evaporated

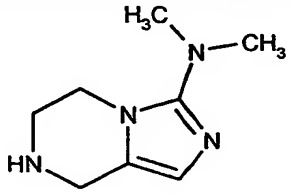
under reduced pressure, and the residual solid was dissolved in 2N hydrochloric acid (10mL), the solution heated under reflux for 2 hours, then cooled and vaporated under reduced pressure. The residual orange gum was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0 to 90:10:1) to give the title compound as an orange solid, 68mg.

^{1}H-nmr (CD_3OD, 400MHz) δ: 1.24 (t, 3H), 2.67 (q, 2H), 3.15 (t, 2H), 3.88 (t, 2H), 3.95 (s, 2H), 6.59 (s, 1H).

LRMS : m/z (ES^+) 138 [MH^+]

Preparation 132

N,N-Dimethyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine



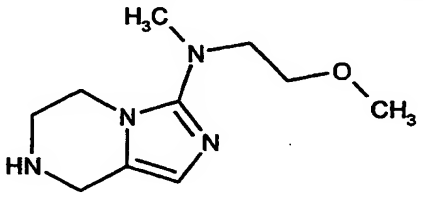
Ammonium formate (2.0g, 31.7mmol) and 10% palladium on charcoal (200mg) were added to a solution of the protected amine from preparation 85 (170mg, 0.66mmol) in ethereal hydrochloric acid (2mL, 1M) and methanol (20mL), and the mixture heated under reflux for 20 minutes. The cooled mixture was diluted with dichloromethane (50mL), filtered through Arbocel®, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1) as eluant to afford the title compound as a colourless gum, 72mg.

^{1}H-nmr ($CDCl_3$, 400MHz) : 1.70 (bs, 1H), 2.74 (s, 6H), 3.13 (t, 2H), 3.73 (t, 2H), 3.98 (s, 2H), 6.46 (s, 1H).

LRMS : m/z (ES^+) 167 [MH^+]

Preparation 133

N-(2-Methoxyethyl)-*N*-m thyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine



The title compound was obtained as a yellow oil, from the protected amine from preparation 86, following the procedure described in preparation 132.

^{1}H-nmr ($CDCl_3$, 400MHz) δ: 2.78 (s, 3H), 3.13 (t, 2H), 3.18 (t, 2H), 3.32 (s, 3H), 3.48 (t, 2H), 3.76 (t, 2H), 3.97 (t, 2H), 6.48 (s, 1H).

LRMS : m/z (ES^+) 211 [MH^+]

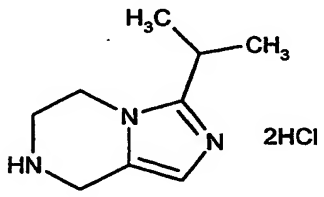
Preparation 134

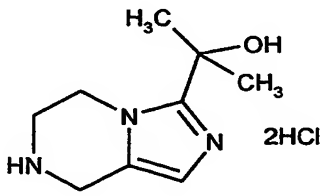
3-Isopropyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine dihyrochloride

and

Preparation 135

2-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyrazin-3-yl)-2-propanol dihydrochloride



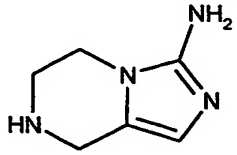


A mixture of the compounds from preparations 87 and 88 (460mg, 1.47mmol), glacial acetic acid (0.5mL) and 10% palladium on charcoal (300mg) was hydrogenated at 50 psi and 70°C for 36 hours. The cooled mixture was diluted with water (10mL), filtered through Arbocel®, washing through with methanol (500mL). The filtrate was evaporated under reduced pressure, and the residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0 to 92:8:1) to give an orange oil. This was dissolved in methanol, 1N ethereal hydrochloric acid added, and the mixture evaporated under reduced pressure to give a mixture of the title compounds as a light brown foam, 165mg.

^{1}H-nmr (CD_3OD, 400MHz) δ: 1.42 (d, 6H), *1.71 (s, 6H),* 3.45 (m, 1H), 3.78 (m, 2H), *3.78 (m, 2H), 4.50 (m, 2H),* 4.58 (m, 2H), *4.58 (m, 2H),* 4.80 (m, 2H), 7.46 (s, 1H).

Preparation 136

5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyrazin-3-amine



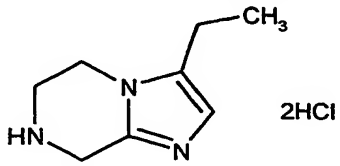
10% Palladium on charcoal (200mg) and ammonium formate (2g) were added carefully to a solution of the compound from preparation 84 (152mg, 0.6mmol) in 1N ethereal hydrochloric acid (2mL) and methanol (20mL). The mixture was heated under reflux for 1.5 hours, then cooled. Additional 1N ethereal hydrochloric acid (1mL), 10% palladium on charcoal (200mg) and ammonium formate (2g) were added, and the mixture heated under reflux for a further 20 minutes. The cooled mixture was diluted with dichloromethane (50mL), filtered through Arbocel®, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1 to 80:20:2) to afford the titl compound as an oil, 35mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 3.12 (t, 2H), 3.57 (t, 2H), 3.87 (s, 2H), 6.27 (s, 1H).

LRMS : m/z (ES^+) 139 [MH^+]

Preparation 137

3-Ethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine dihydrochloride



A mixture of the protected amine from preparation 92 (605mg, 2.12mmol), acetic acid (8mL), and 1N ethereal hydrobromic acid (30mL) in toluene (25mL) was stirred at 100°C for 4 hours. The mixture was cooled, concentrat d under reduced pressure, and azeotroped with toluene (2x25mL). The residue was dissolved in

1N ethereal hydrochloic acid, th n evaporated under reduced pressure to afford the title compound as a tan coloured solid, 405mg.

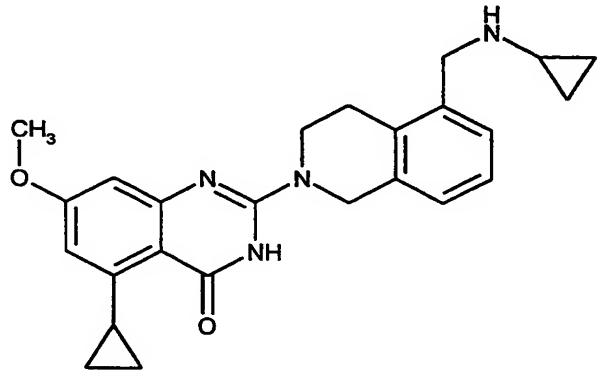
^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.10 (t, 3H), 2.60 (m, 2H), 3.60 (m, 2H), 4.32 (m, 2H) 4.62 (s, 2H), 7.50 (s, 1H).

LRMS : m/z (ES$^+$) 152 [MH$^+$]

The invention is illustrated by the following examples:

Example 1

5-Cyclopropyl-2-(5-[(cyclopropylamino)methyl]-3,4-dihydro-2(1*H*)-isoquinolinyl)-7-methoxy-4(3*H*)-quinazolinone



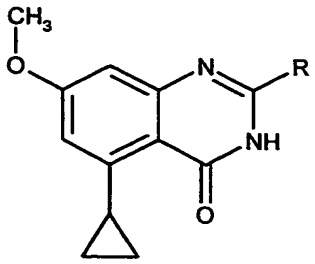
A mixture of the amine hydrochloride from preparation 95 (113mg, 0.41mmol), the chloride from preparation 18 (86mg, 0.34mmol) and diisopropylethylamine (0.36mL, 1.7mmol) in n-butanol (3mL) was stirred under reflux for 2.5 hours. The cooled reaction mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane (40mL) and water. The layers were separated, the organic phase washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol (97:3) as eluant to afford the title compound as a solid.

^{1}Hnmr (DMSOd_6, 400MHz) δ: 0.13 (m, 2H), 0.35 (m, 2H), 0.63 (m, 2H), 0.90 (m, 2H), 2.07 (m, 2H), 2.90 (m, 2H), 3.49 (m, 1H), 3.68 (s, 2H), 3.75 (m, 4H), 3.83 (m, 2H), 4.75 (s, 2H), 6.13 (m, 1H), 6.48 (m, 1H), 7.05 (m, 1H), 7.15 (m, 1H), 10.82 (bs, 1H).

LRMS : m/z (ES$^+$) 417 [MH$^+$]

Microanalysis found: C, 69.56; H, 6.54; N, 13.04. $C_{25}H_{28}N_4O_2$;$0.8H_2O$ requires C, 69.69; H, 6.92; N, 13.00%.

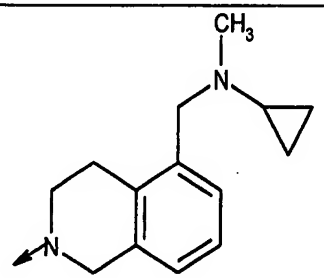
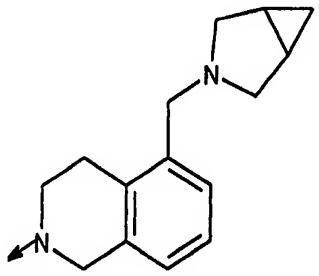
Examples 2 to 25

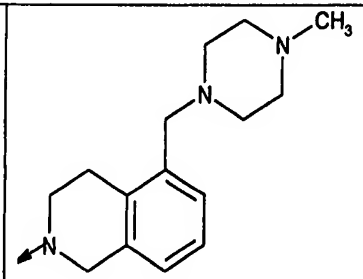
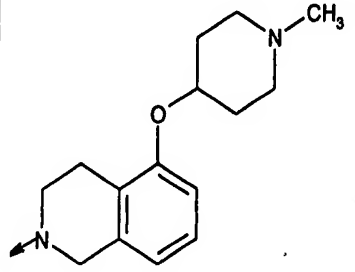
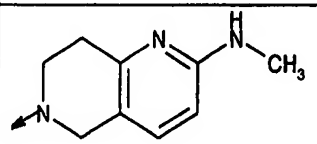


General Method

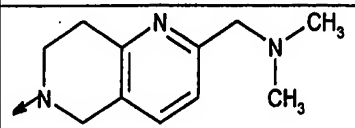
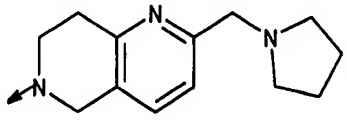
To a solution of the chloro-quinazolinone from preparation 18 (1eq) in n-butanol (15mL per mmol) under nitrogen was added diisopropylethylamine (A) or triethylamine (B) (1.7-8eq) and the appropriate secondary amine (1-2eq). The resultant mixture was then heated at reflux for 1-6 hours, cooled and the product was isolated by filtration, washing with n-butanol and diethyl ether.

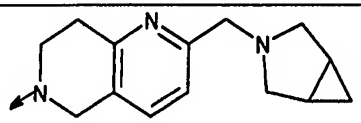
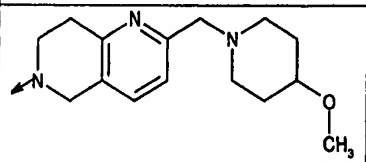
Some products (a) were additionally purified by column chromatography on silica gel using dichloromethane:methanol or dichloromethane:methanol:0.88 ammonia as eluants.

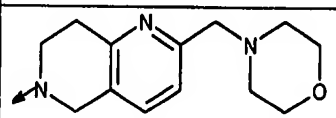
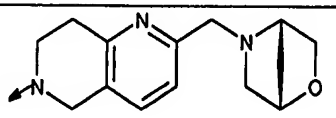
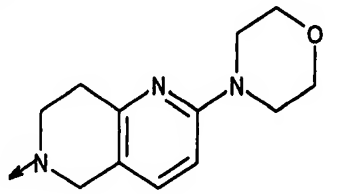
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
2(a)		A	29 white solid	^{1}Hnmr (DMSOd_6, 400MHz) δ: 0.30 (m, 2H), 0.40 (m, 2H), 0.63 (m, 2H), 0.94 (m, 2H), 1.73 (m, 1H), 2.10 (s, 3H), 2.90 (m, 2H), 3.46 (m, 1H), 3.60 (s, 2H), 3.77 (s, 3H), 3.80 (m, 2H), 4.77 (s, 2H), 6.13 (s, 1H), 6.53 (s, 1H), 7.10 (m, 3H), 10.84 (bs, 1H). LRMS : m/z (ES^+) 453 [MNa^+] Microanalysis found: C, 72.07; H, 7.00; N, 12.94. $C_{26}H_{30}N_4O_2$;0.2H_2O requires C, 71.93; H, 7.06; N, 12.90%.
3		B	76 white powder	^{1}Hnmr (DMSOd_6, 400MHz) δ: 0.27 (m, 1H), 0.57 (m, 1H), 0.63 (m, 2H), 0.94 (m, 2H), 1.35 (m, 2H), 2.31 (m, 2H), 2.77 (d, 2H), 2.86 (m, 2H), 3.50 (m, 3H), 3.74 (s, 3H), 3.80 (m, 2H), 4.76 (s, 2H), 6.13 (s, 1H), 6.32 (s, 1H), 7.10 (m, 3H), 10.97 (bs, 1H). LRMS : m/z (ES^+) 465 [MNa^+] Microanalysis found: C, 72.83; H, 6.83; N, 12.52. $C_{27}H_{30}N_4O_2$;0.1C_4H_9OH requires C, 73.14; H, 6.94; N, 12.45%.

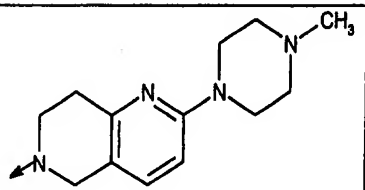
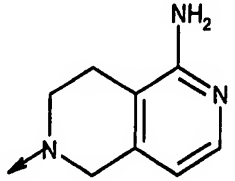
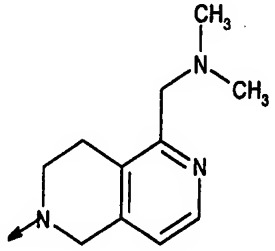
4		A	88 white solid	^{1}Hnmr ($CDCl_3$, 400MHz) δ: 0.70 (m, 2H), 0.97 (m, 2H), 2.26 (s, 3H), 2.44 (m, 8H), 3.06 (t, 2H), 3.41 (m, 1H), 3.46 (s, 2H), 3.85 (s, 3H), 3.91 (t, 2H), 4.87 (s, 2H), 6.29 (s, 1H), 6.67 (d, 1H), 7.11 (dd, 1H), 7.15 (d, 2H), 10.01 (bs, 1H). LRMS : m/z (ES^+) 482 [MNa^+]
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
5(a)		A	43 white solid	^{1}Hnmr ($DMSOd_6$, 400MHz) δ: 0.64 (m, 2H), 0.90 (m, 2H), 1.67 (m, 2H), 1.87 (m, 2H), 2.17 (s, 3H), 2.25 (m, 2H), 2.47 (s, 3H), 2.65 (m, 2H), 2.74 (t, 2H), 3.49 (m, 1H), 3.83 (t, 2H), 4.37 (m, 1H), 4.73 (s, 2H), 6.13 (s, 1H), 6.52 (s, 1H), 6.75 (d, 1H), 6.83 (d, 1H), 7.11 (dd, 1H), 11.00 (bs, 1H). LRMS : m/z (ES^+) 461 [MH^+] Microanalysis found: C, 69.55; H, 7.09; N, 11.78. $C_{27}H_{32}N_4O_3$;0.3H_2O requires C, 69.59; H, 7.05; N, 12.02%.
6		B	86 white powder	^{1}Hnmr ($DMSOd_6$, 400MHz) δ: 0.62 (m, 2H), 0.91 (m, 2H), 2.75 (m, 5H), 3.50 (m, 1H), 3.77 (s, 3H), 3.86 (t, 2H), 4.58 (s, 2H), 6.13 (s, 1H), 6.25 (m, 1H), 6.31 (d, 1H), 6.53 (s, 1H), 7.19 (d, 1H), 10.99 (bs, 1H). LRMS : m/z (ES^+) 400 [MNa^+] Microanalysis found: C, 65.18; H, 6.03; N, 18.03.

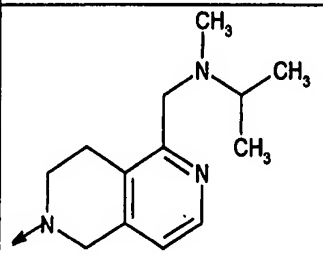
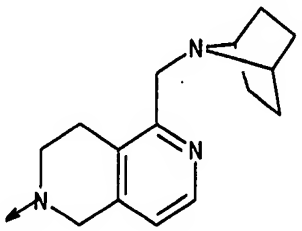
				$C_{21}H_{23}N_5O_2.0.5H_2O$ requires C, 65.27; H, 6.26; N, 18.12%.

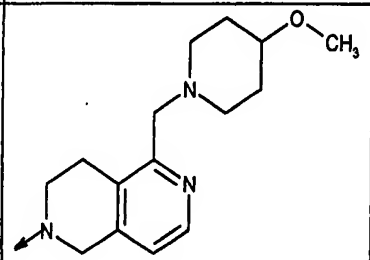
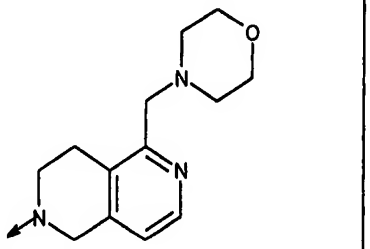
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
7(a)		A	35 white solid	^{1}H-nmr (DMSO-d_6, 400 MHz) δ : 0.64 (m, 2H), 0.93 (m, 2H), 2.16 (s, 6H), 2.93 (t, 2H), 3.47 (m, 3H), 3.76 (s, 3H), 3.93 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.53 (s, 1H), 7.24 (d, 1H), 7.57 (d, 1H), 11.08 (bs, 1H). LRMS : m/z (ES^-) 404 [$M-H^-$] Microanalysis found: C, 67.08; H, 6.72; N, 16.98. $C_{23}H_{27}N_5O_2$;0.3H_2O requires C, 67.23; H, 6.77; N, 17.04%.
8(a)		A	51 white solid	^{1}H-nmr (DMSO-d_6, 400 MHz) δ : 0.64 (m, 2H), 0.93 (m, 2H), 1.70 (m, 4H), 2.53 (m, 4H), 2.94 (t, 2H), 3.50 (m, 1H), 3.69 (s, 2H), 3.76 (s, 3H), 3.93 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.52 (s, 1H), 7.25 (d, 1H), 7.56 (d, 1H), 11.08 (bs, 1H). LRMS : m/z (ES^+) 454 [MNa^+] Microanalysis found: C, 66.72; H, 6.63; N, 15.41. $C_{25}H_{29}N_5O_2$;0.9H_2O requires C, 67.06; H, 6.93; N, 15.64%.

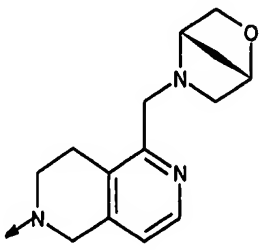
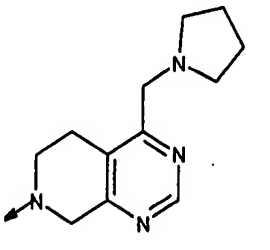
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
9(a)		B	31	^{1}H-nmr (DMSO-d_6, 400 MHz) δ : 0.32 (m, 1H), 0.63 (m, 3H), 0.93 (m, 2H), 1.35 (m, 2H), 2.37 (m, 2H), 2.90 (m, 4H), 3.49 (m, 1H), 3.63 (s, 2H), 3.78 (s, 3H), 3.92 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.53 (s, 1H), 7.18 (d, 1H), 7.57 (d, 1H), 11.05 (bs, 1H). LRMS : m/z (ES$^+$) 466 [MNa$^+$] Microanalysis found: C, 69.91; H, 6.57; N, 15.67. $C_{26}H_{29}N_5O_2$;0.2H_2O requires C, 69.84; H, 6.63; N, 15.66%.
10 (b)		A	83 white solid	^{1}H-nmr (DMSO-d_6, 400 MHz) δ : 0.62 (m, 2H), 0.94 (m, 2H), 1.40 (m, 2H), 1.80 (m, 2H), 2.16 (m, 2H), 2.62 (m, 2H), 2.96 (m, 2H), 3.16 (m, 1H), 3.20 (s, 3H), 3.50 (s, 2H), 3.78 (s, 3H), 3.96 (m, 2H), 4.22 (m, 1H), 4.78 (s, 2H), 6.18 (m, 1H), 6.56 (bs, 1H), 7.24 (d, 1H), 7.58 (d, 1H), 11.00 (bs, 1H). LRMS : m/z (ES$^+$) 477 [MH$^+$] Microanalysis found: C, 67.22; H, 6.96; N, 14.40. $C_{27}H_{33}N_5O_3$;0.5C_2H_5OH requires C, 67.45; H, 7.28; N, 14.05%.

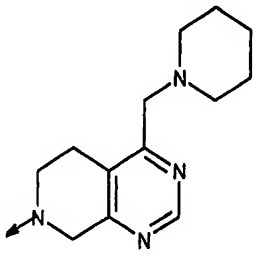
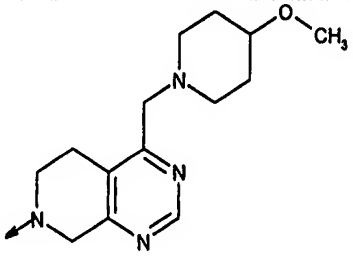
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
11 (a)		A	44 white solid	^{1}H-nmr (DMSO-d_6, 400 MHz) δ : 0.65 (m, 2H), 0.91 (m, 2H), 2.38 (m, 4H), 2.93 (t, 2H), 3.51 (m, 3H), 3.55 (m, 4H), 3.76 (s, 3H), 3.92 (t, 2H), 4.77 (s, 2H), 6.14 (s, 1H), 6.52 (s, 1H), 7.27 (d, 1H), 7.56 (d, 1H), 11.58 (bs, 1H). LRMS : m/z (ES$^+$) 470 [MNa$^+$] Microanalysis found: C, 66.00; H, 6.49; N, 15.35. $C_{25}H_{29}N_5O_3$;0.5CH_3OH requires C, 66.07; H, 6.74; N, 15.11%.
12		A	66 solid	^{1}H-nmr (DMSO-d_6, 400 MHz) δ : 0.66 (m, 2H), 0.93 (m, 2H), 1.59 (d, 1H), 1.80 (d, 1H), 2.45 (d, 1H), 2.76 (d, 1H), 2.94 (t, 2H), 3.47 (s, 1H), 3.52 (d, 2H), 3.77 (m, 5H), 3.91 (d, 1H), 3.95 (t, 2H), 4.33 (s, 1H), 4.78 (s, 2H), 6.14 (d, 1H), 6.53 (d, 1H), 7.29 (d, 1H), 7.56 (d, 1H), 11.09 (bs, 1H). LRMS : m/z (ES$^+$) 460 [MH$^+$] Microanalysis found: C, 67.96; H, 6.38; N, 15.12. $C_{28}H_{29}N_5O_3$ requires C, 67.67; H, 6.38; N, 15.12%.
13		B	solid	^{1}H-nmr ($CDCl_3$, 400 MHz) δ : 0.70 (m, 2H), 1.00 (m, 2H), 2.96 (t, 2H), 3.38 (m, 1H), 3.48 (m, 4H), 3.79 (m, 4H), 3.83 (s, 3H), 3.94 (t, 2H), 4.69 (s, 2H), 6.29 (s, 1H), 6.51 (d, 1H), 6.64 (s, 1H), 7.30 (d, 1H), 9.22 (bs, 1H).

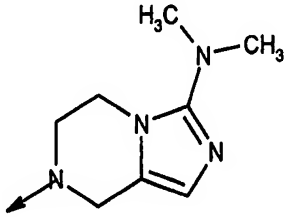
				LRMS : m/z (ES^+) 456 [MNa^+]
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
14 (a)		A	62 solid	^{1}H-nmr ($CDCl_3$, 400 MHz) δ : 0.71 (m, 2H), 0.99 (m, 2H), 2.34 (s, 3H), 2.51 (m, 4H), 2.97 (t, 2H), 3.38 (m, 1H), 3.43 (m, 4H), 3.82 (s, 3H), 3.98 (t, 2H), 4.73 (s, 2H), 6.27 (s, 1H), 6.52 (d, 1H), 6.64 (s, 1H), 7.24 (m, 1H), 9.60 (bs, 1H). LRMS : m/z (ES^+) 469 [MNa^+]
15		A	86 off-white solid	^{1}H-nmr ($CDCl_3$, 400 MHz) δ : 0.72 (m, 2H), 1.00 (m, 2H), 2.63 (t, 2H), 3.37 (m, 1H), 3.85 (s, 3H), 3.97 (t, 2H), 4.39 (bs, 2H), 4.73 (s, 2H), 6.31 (d, 1H), 6.52 (m, 3H), 6.66 (d, 1H), 7.92 (d, 1H). LRMS : m/z (ES^+) 364 [MH^+]
16		A	66 solid	^{1}H-nmr ($CDCl_3$, 400 MHz) δ : 0.74 (m, 2H), 0.98 (m, 2H), 2.24 (s, 6H), 3.09 (m, 2H), 3.42 (m, 1H), 3.54 (s, 2H), 3.86 (s, 3H), 4.01 (t, 2H), 4.90 (s, 2H), 6.31 (d, 1H), 6.68 (d, 1H), 7.01 (d, 1H), 8.36 (d, 1H), 10.96 (bs, 1H). LRMS : m/z (ES^+) 406 [MH^+] Microanalysis found: C, 67.92; H, 6.73; N, 17.23. $C_{23}H_{27}N_5O_2$ requires C, 68.13; H, 6.71; N, 17.27%.

Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
17		B	50 white solid	^{1}H-nmr ($CDCl_3$, 400 MHz) δ : 0.63 (m, 2H), 0.91 (m, 2H), 0.98 (d, 6H), 1.97 (s, 3H), 2.80 (m, 1H), 3.00 (m, 2H), 3.51 (m, 1H), 3.61 (s, 2H), 3.77 (s, 3H), 3.85 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.54 (s, 1H), 7.13 (d, 1H), 8.22 (d, 1H), 11.12 (bs, 1H). LRMS : m/z (ES^-) 432 [$M-H^-$] Microanalysis found: C, 68.41; H, 7.23; N, 15.76. $C_{25}H_{31}N_5O_2$;0.25H_2O requires C, 68.55; H, 7.25; N, 15.99%.
18		B	61 white solid	^{1}H-nmr ($CDCl_3$, 400 MHz) δ : 0.74 (m, 2H), 0.98 (m, 2H), 1.26 (d, 4H), 1.77 (m, 4H), 3.19 (m, 4H), 3.41 (m, 1H), 3.65 (s, 2H), 3.86 (s, 3H), 3.97 (t, 2H), 4.89 (s, 2H), 6.31 (d, 1H), 6.67 (d, 1H), 7.01 (d, 1H), 8.33 (d, 1H), 10.44 (bs, 1H). LRMS : m/z (ES^-) 456 [$M-H^-$] Microanalysis found: C, 70.41; H, 6.80; N, 15.13. $C_{27}H_{31}N_5O_2$;0.25H_2O requires C, 70.18; H, 6.87; N, 15.16%.

Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
19		A	38 white solid	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.73 (m, 2H), 0.99 (m, 2H), 1.25 (s, 1H), 1.85 (m, 2H), 2.16 (m, 3H), 2.70 (m, 2H), 3.12 (t, 2H), 3.20 (m, 1H), 3.31 (s, 3H), 3.40 (m, 1H), 3.62 (s, 2H), 3.85 (s, 3H), 3.93 (t, 2H), 4.87 (s, 2H), 6.32 (d, 1H), 6.88 (d, 1H), 7.02 (d, 1H), 8.36 (d, 1H). LRMS : m/z (ES^+) 476 [MH^+] Microanalysis found: C, 66.97; H, 7.00; N, 14.19. $C_{27}H_{33}N_5O_3$;0.50H_2O requires C, 66.92; H, 7.07; N, 14.45%.
20 (a)		B	91 white solid	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.76 (m, 2H), 0.99 (m, 2H), 2.47 (m, 4H), 3.11 (t, 2H), 3.43 (m, 1H), 3.64 (s, 2H), 3.67 (m, 4H), 3.87 (s, 3H), 4.01 (t, 2H), 4.92 (s, 2H), 6.32 (s, 1H), 6.68 (s, 1H), 7.04 (d, 1H), 8.37 (d, 1H), 10.78 (bs, 1H). LRMS : m/z (ES^+) 448 [MH^+] Microanalysis found: C, 66.60; H, 6.51; N, 15.63. $C_{25}H_{29}N_5O_3$;0.20H_2O requires C, 66.56; H, 6.59; N, 15.52%.

Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
21 (a)		A	25 yellow oil	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.78 (m, 2H), 1.00 (m, 2H), 1.52-1.80 (m, 4H), 1.98 (m, 1H), 2.78 (m, 1H), 2.98 (m, 1H), 3.18 (m, 2H), 3.42 (m, 1H), 3.63 (m, 1H), 3.90 (s, 3H), 4.00 (m, 2H), 4.17 (m, 1H), 4.42 (m, 1H), 4.90 (s, 2H), 6.35 (d, 1H), 6.67 (d, 1H), 7.02 (d, 1H), 8.37 (d, 1H). LRMS : m/z (ES^-) 458 [M-H-] Microanalysis found: C, 67.48; H, 6.40; N, 15.10. $C_{28}H_{29}N_5O_3$; requires C, 67.96; H, 6.36; N, 15.24%.
22 (a)		A	54 off-white solid	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.73 (m, 2H), 1.00 (m, 2H), 1.78 (m, 4H), 2.57 (m, 4H), 3.04 (t, 2H), 3.45 (m, 1H), 3.72 (s, 2H), 3.85 (s, 3H), 4.08 (t, 2H), 4.98 (s, 2H), 6.34 (d, 1H), 6.68 (d, 1H), 8.95 (s, 1H), 11.32 (bs, 1H). LRMS : m/z (ES^+) 433 [MH^+] Microanalysis found: C, 66.23; H, 6.50; N, 19.21. $C_{24}H_{28}N_6O_2$ requires C, 66.65; H, 6.53; N, 19.43%.

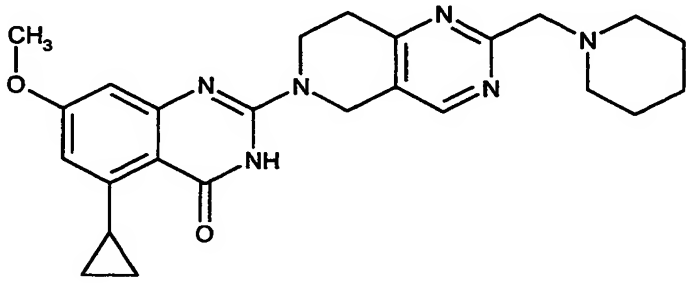
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
23		A	38 white solid	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.73 (m, 2H), 0.99 (m, 2H), 1.42 (m, 2H), 1.54 (m, 4H), 2.40 (m, 4H), 3.09 (t, 2H), 3.43 (m, 1H), 3.54 (s, 2H), 3.85 (s, 3H), 4.05 (t, 2H), 4.96 (s, 2H), 6.34 (d, 1H), 6.67 (d, 1H), 8.94 (s, 1H), 10.85 (bs, 1H). LRMS : m/z (ES^+) 447 [MH^+] Microanalysis found: C, 66.96; H, 6.82; N, 18.63. $C_{25}H_{30}N_6O_2$ requires C, 67.24; H, 6.77; N, 18.82%.
24		A	73 solid	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.73 (m, 2H), 1.01 (m, 2H), 1.55 (m, 2H), 1.84 (m, 2H), 2.23 (m, 2H), 2.71 (m, 2H), 3.07 (t, 2H), 3.22 (m, 1H), 3.31 (s, 3H), 3.42 (m, 1H), 3.57 (s, 2H), 3.85 (s, 3H), 4.06 (t, 2H), 4.97 (s, 2H), 6.34 (d, 1H), 6.67 (d, 1H), 8.94 (s, 1H), 10.96 (bs, 1H). LRMS : m/z (ES^+) 477 [MH^+] Microanalysis found: C, 63.66; H, 6.62; N, 17.13. $C_{26}H_{32}N_6O_3$;0.75H_2O requires C, 63.72; H, 6.89; N, 17.15%.

Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical Data
25		A	59 white solid	^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.74 (m, 2H), 1.00 (m, 2H), 2.79 (s, 6H), 3.36 (m, 1H), 3.85 (s, 3H), 3.95 (t, 2H), 4.09 (t, 2H), 4.89 (s, 2H), 6.34 (d, 1H), 6.56 (s, 1H), 6.65 (d, 1H), 10.81 (bs, 1H). LRMS : m/z (ES^+) 381 [MH^+] Microanalysis found: C, 61.81; H, 6.25; N, 21.47. $C_{20}H_{24}N_6O_2$;0.5H_2O requires C, 61.68; H, 6.47; N, 21.58%.

(b)-ethanol was used as a co-solvent in the reaction

Example 26

5-Cyclopropyl-7-methoxy-2-(2-(1-piperidinylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-4(3*H*)-quinazolinone



A mixture of the chloride from preparation 18 (302mg, 1.2mmol), the amine from preparation 124 (1.23mmol) and diisopropylethylamine (646mg, 5mmol) in n-butanol (10mL) was heated under reflux for 1.5 hours. The cooled mixture was diluted with water and extracted with dichloromethane (3x50mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 90:10) to afford the title compound as an off-white solid, 307mg.

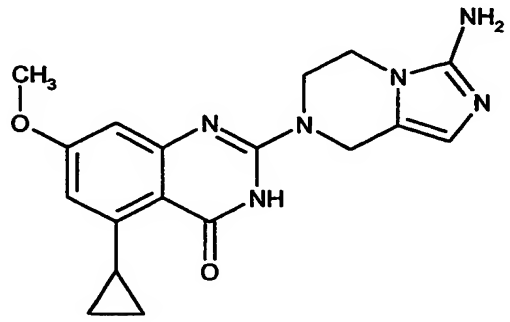
^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.72 (m, 2H), 0.96 (m, 2H), 1.48 (m, 2H), 1.71 (m, 4H), 2.70 (m, 4H), 3.07 (t, 2H), 3.53 (m, 1H), 3.84 (s, 3H), 3.88 (bs, 2H), 4.06 (t, 2H), 4.89 (s, 2H), 6.31 (s, 1H), 6.66 (s, 1H), 8.51 (s, 1H), 11.12 (bs, 1H).

LRMS : m/z (ES^+) 447 [MH^+]

Microanalysis found: C, 65.74; H, 6.83; N, 18.28. $C_{25}H_{30}N_6O_2$;0.5H_2O requires C, 65.91; H, 6.86; N, 18.45%.

Example 27

2-(3-Amino-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-5-cyclopropyl-7-methoxy-4(3*H*)-quinazolinone



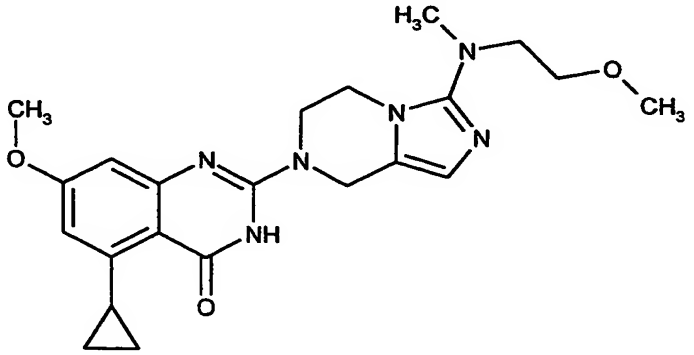
The title compound was obtained as a yellow solid in 23% yield, from the chlorid from preparation 18 and the amine from preparation 136, following a similar procedure to that described in example 26, except dichloromethane:methanol:0.88 ammonia (90:10:1) was used as the column eluant.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ : 0.64 (m, 2H), 0.2 (m, 2H), 3.48 (m, 1H), 3.75 (m, 5H), 3.93 (t, 2H), 4.68 (s, 2H), 5.48 (s, 2H), 6.16 (s, 1H), 6.28 (s, 1H), 6.53 (s, 1H), 11.10 (bs, 1H).

LRMS : m/z (ES^+) 353 [MH^+]

Exampl 28

5-Cyclopropyl-7-methoxy-2-(3-[(2-methoxyethyl)(methyl)amino]-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-4(3*H*)-quinazolinone



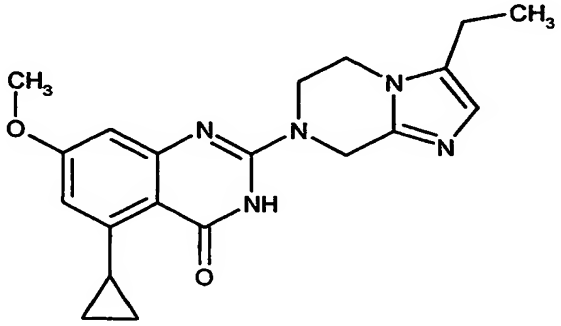
The title compound was obtained as a white solid in 45% yield, from the chloride from preparation 18 and the amine from preparation 133, following a similar procedure to that described in example 26.

^{1}H-nmr ($CDCl_3$, 400MHz) δ : 0.73 (m, 2H), 0.96 (m, 2H), 2.82 (s, 3H), 3.21 (t, 2H), 3.49 (m, 1H), 3.50 (s, 3H), 3.51 (t, 2H), 3.84 (s, 3H), 3.96 (t, 2H), 4.09 (t, 2H), 4.91 (s, 2H), 6.33 (d, 1H), 6.55 (s, 1H), 6.65 (d, 1H), 11.38 (bs, 1H).

LRMS : m/z (ES^+) 425 [MH^+]

Example 29

5-Cyclopropyl-2-(3-ethyl-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-7-methoxy-4(3*H*)-quinazolinone



The title compound was obtained as a white solid in 43% yield, from the chloride from preparation 18 and the amine from preparation 131, following a similar procedure to

that described in example 26, except dichloromethan :methanol:0.88 ammonia (95:50.5) was used as the column eluant.

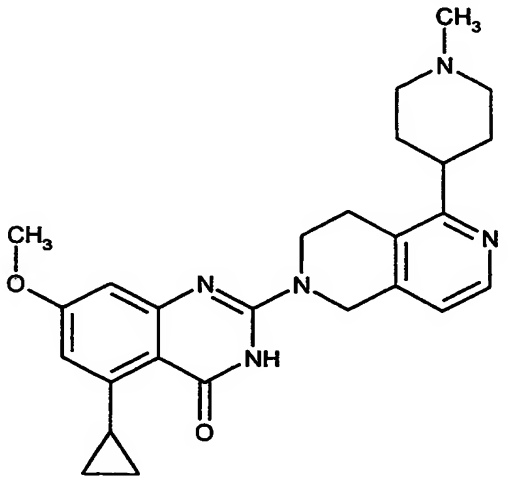
^{1}H-nmr (DMSOd_6, 400MHz) δ : 0.62 (m, 2H), 0.96 (m, 2H), 1.16 (t, 3H), 2.52 (m, 2H), 3.50 (m, 1H), 3.78 (s, 3H), 3.92 (m, 2H), 4.04 (m, 2H), 4.78 (s, 2H), 6.18 (s, 1H), 6.56 (s, 1H), 6.60 (s, 1H), 10.80, 11.25 (2xbs, 1H).

LRMS : m/z (ES$^+$) 366 [MH$^+$]

Microanalysis found: C, 64.26; H, 6.31; N, 18.10. $C_{20}H_{23}N_5O_2$;0.15CH_2Cl_2 requires C, 64.00; H, 6.21; N, 18.52%.

Example 30

5-Cyclopropyl-7-methoxy-2-(5-(1-methyl-4-piperidinyl)-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone



A mixture of the chloride from preparation 18 (0.40mmol), the amine hydrochloride from preparation 120 (145.6mg, 0.48mmol) and triethylamine (223μl, 1.60mmol) in n-butanol (6mL) was heated under reflux for 3 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between water (4mL) with saturated sodium bicarbonate solution (2mL), and dichloromethane (30mL), and the layers separated. The aqueous phase was extracted with further dichloromethane (2x20mL), and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residual solid was purified by column

chromatography on silica gel using an elution gradient of dichloromethan :m thanol:0.88 ammonia (95:5:0.2 to 90:10:0.6) to afford the title compound as a white solid, 110mg.

^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 0.64 (m, 2H), 0.93 (m, 2H), 1.60 (m, 2H), 1.83 (m, 2H), 2.04 (m, 2H), 2.21 (s, 3H), 2.80 (m, 1H), 2.87 (m, 4H), 3.40 (m, 1H), 3.76 (s, 3H), 3.89 (t, 2H), 4.77 (s, 2H), 6.15 (s, 1H), 6.51 (d, 1H), 7.04 (d, 1H), 8.30 (d, 1H), 11.07 (bs, 1H).

LRMS : m/z (ES^+) 446 [MH^+]

Microanalysis found: C, 68.43; H, 7.11; N, 15.35. $C_{26}H_{31}N_5O_2$;0.6H_2O requires C, 70.09; H, 7.11; N, 15.35%.

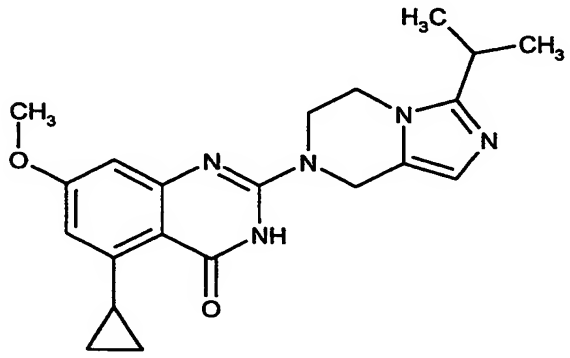
Example 31

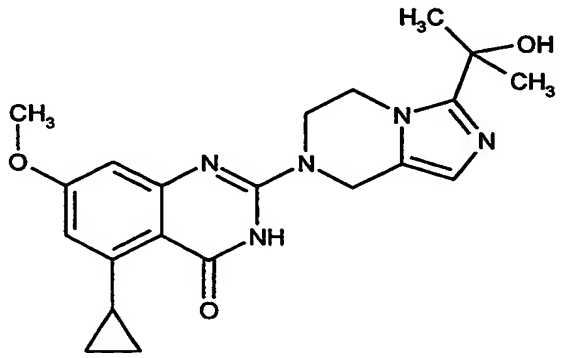
5-Cyclopropyl-2-(3-isopropyl-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-7-methoxy-4(3*H*)-quinazolinone

and

Example 32

5-Cyclopropyl-2-(3-(1-hydroxy-1-methylethyl)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-7-methoxy-4(3*H*)-quinazolinone





A mixture of the chloride from preparation 18 (80mg, 0.32mmol), the amines from preparations 120 and 121 (99mg), and triethylamine (178μl, 1.28mmol) in n-butanol (6mL) was heated under reflux for 3.5 hours. The cooled mixture was concentrated under reduced pressure and the solid residue partitioned between dichloromethane (30mL) and a solution of saturated sodium bicarbonate (1mL) in water (5mL), and the

phases separated. The aqueous layer was extracted with dichloromethane (2x30mL), and th combined organic extracts dried ($MgSO_4$) and vaporated und r reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound of example 31, 42mg.

^{1}H-nmr (CD_3OD, 400MHz) δ: 0.65 (m, 2H), 0.97 (m, 2H), 1.28 (d, 6H), 3.10 (m, 1H), 3.33 (s, 1H), 3.82 (s, 3H), 4.07 (m, 2H), 4.13 (t, 2H), 4.84 (s, 2H), 6.34 (d, 1H), 6.70 (d, 1H), 6.75 (s, 1H).

LRMS : m/z (ES^+) 380 [MH^+]

Microanalysis found: C, 65.77; H, 6.69; N, 18.46. $C_{21}H_{25}N_5O_2$;0.2H_2O requires C, 65.84; H, 6.68; N, 18.28%.

Further elution gave the title compound of example 32, 40mg.

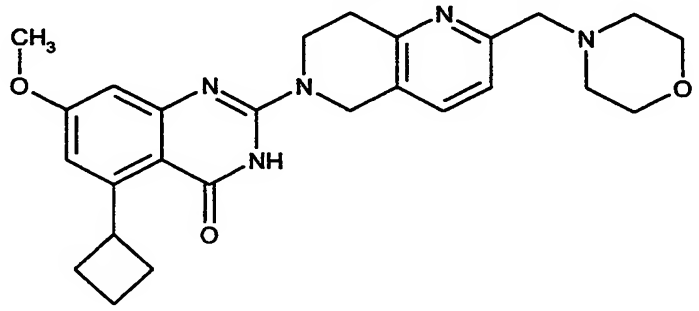
^{1}H-nmr (CD_3OD, 400MHz) δ: 0.62 (m, 2H), 0.97 (m, 2H), 1.56 (s, 6H), 3.29 (m, 1H), 3.82 (s, 3H), 4.00 (m, 2H), 4.53 (m, 2H), 4.84 (s, 2H), 6.34 (s, 1H), 6.70 (s, 1H), 6.75 (s, 1H).

LRMS : m/z (ES^+) 396 [MH^+]

Microanalysis found: C, 63.12; H, 6.59; N, 17.21. $C_{21}H_{25}N_5O_3$;0.07CH_2Cl_2 requires C, 63.05; H, 6.31; N, 17.44%.

Example 33

5-Cyclobutyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone

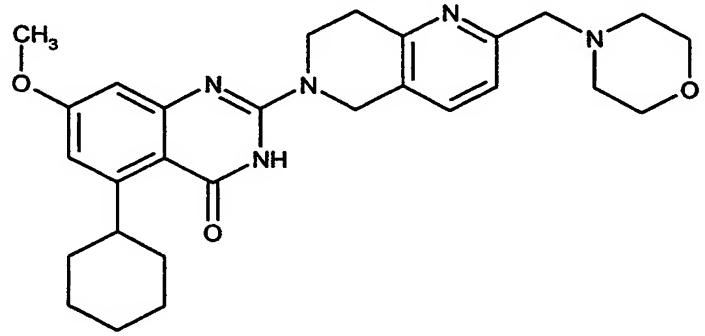


The title compound was obtained as a solid in 74% yield from the compounds from preparation 19 and 106, following the procedure described in example 4.

^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.66-1.75 (m, 1H), 1.83-2.03 (m, 3H), 2.29 (m, 2H), 2.38 (m, 4H), 2.93 (t, 2H), 3.51 (s, 2H), 3.56 (m, 4H), 3.81 (s, 3H), 3.92 (t, 2H), 4.57 (m, 1H), 4.77 (s, 2H), 6.59 (s, 2H), 7.27 (d, 1H), 7.57 (d, 1H), 11.05 (bs, 1H).
LRMS : m/z (ES$^+$) 462 [MH$^+$]
Microanalysis found: C, 67.66; H, 6.78; N, 14.95. $C_{26}H_{31}N_5O_3$ requires C, 67.66; H, 6.77; N, 15.17%.

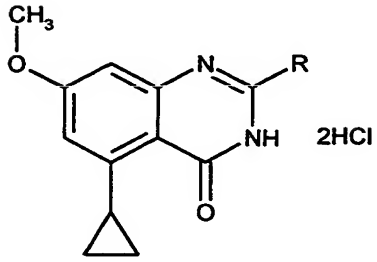
Example 34

5-Cyclohexyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone

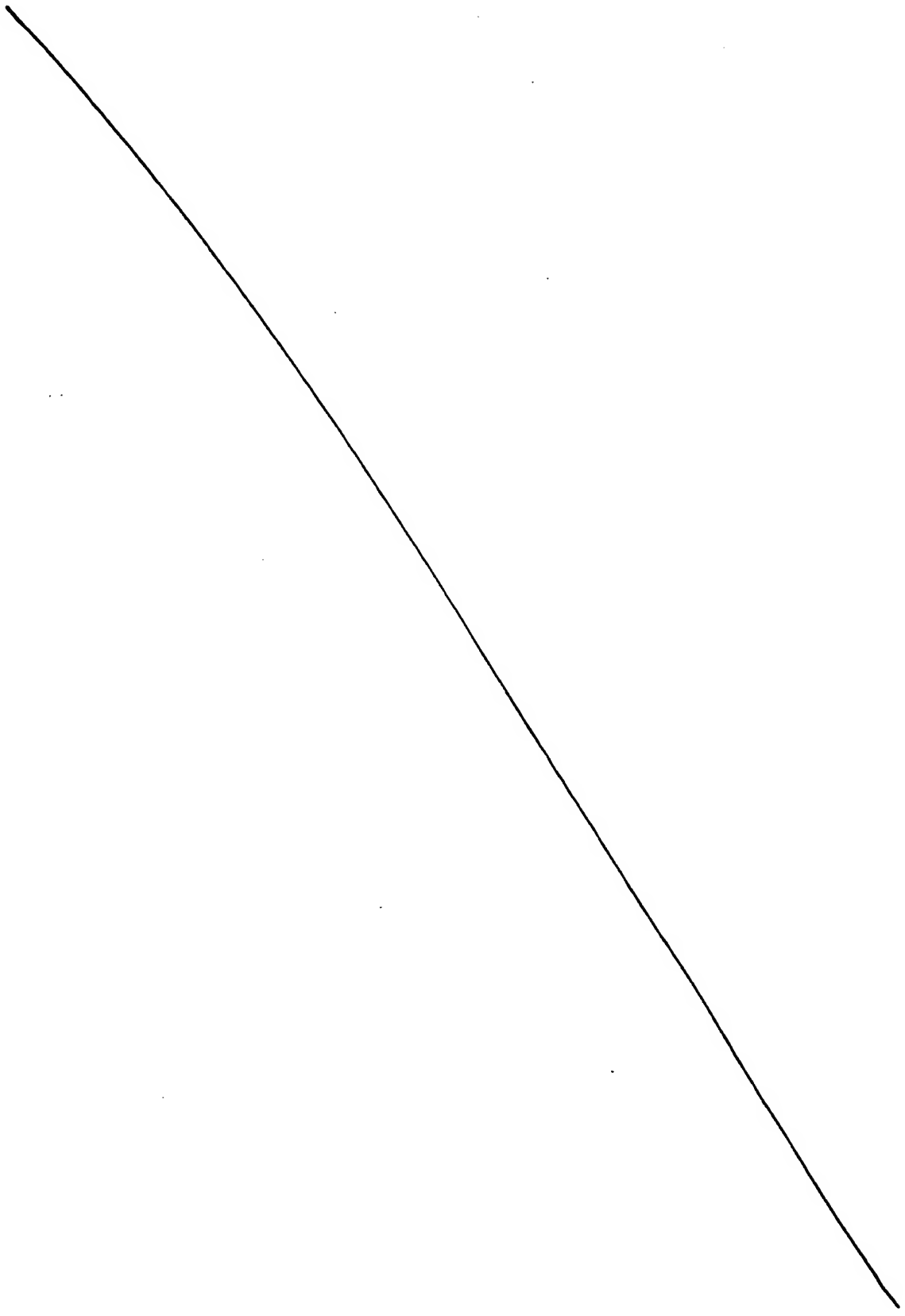


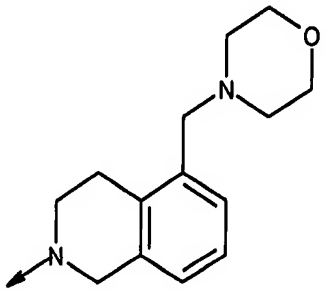
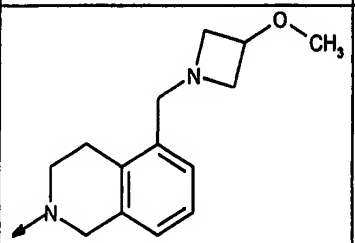
The title compound was obtained as a solid in 70% yield, after recrystallisation from diethyl ether, from the compounds from preparation 20 and 106, following a similar procedure to that described in example 26.
^{1}H-nmr (DMSOd_6, 400MHz) δ: 1.15-1.46 (m, 5H), 1.66-1.84 (m, 5H), 2.38 (m, 4H), 2.94 (t, 2H), 3.52 (s, 2H), 3.57 (m, 4H), 3.79 (s, 3H), 3.93 (t, 2H), 4.14 (t, 1H), 4.77 (s, 2H), 6.57 (m, 2H), 7.27 (d, 1H), 7.57 (d, 1H), 11.03 (bs, 1H).
LRMS : m/z (APCI$^+$) 490 [MH$^+$]
Microanalysis found: C, 68.84; H, 7.33; N, 14.18. $C_{28}H_{35}N_5O_3$ requires C, 68.69; H, 7.21; N, 14.30%.

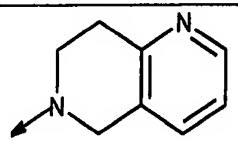
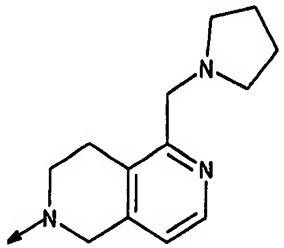
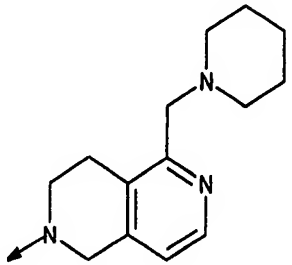
Exampl s 35 to 39



The following examples were prepared following the procedure described for examples 2 to 25. The compounds were then dissolved in a solution of dichloromethane with a minimum volume of methanol, then treated with 1N ethereal hydrochloric acid. The resultant mixture was evaporated under reduced pressure to afford the title compounds.



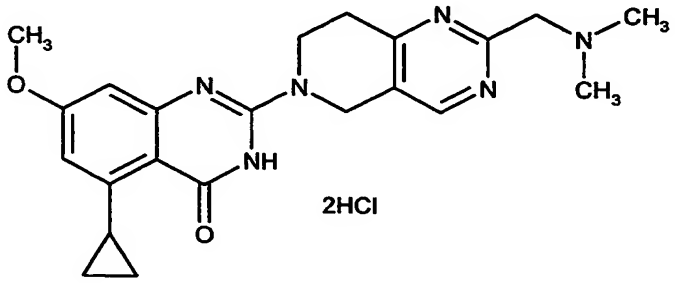
Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical data
35		A	90	^{1}H-nmr (DMSO-d_6, 400MHz) δ : 0.76 (m, 2H), 0.98 (m, 2H), 3.18-3.35 (m, 7H), 3.79 (s, 3H), 3.88 (s, 4H), 4.00 (m, 2H), 4.16 (s, 2H), 4.98 (s, 2H), 6.38 (s, 1H), 7.32 (bs, 2H), 7.46 (bs, 1H), 7.64 (bs, 1H), 11.47 (bs, 1H). LRMS (ES$^+$): m/z (MH^+) 447 Microanalysis: Found: C, 58.41; H, 6.57; N, 10.02. $C_{28}H_{30}N_4O_3$;2HCl;H_2O requires C, 58.10; H, 6.38; N, 10.42%
36 (a)		A	56	^{1}H-nmr (DMSO-d_6, 400MHz) δ : 0.74 (m, 2H), 0.98 (m, 2H), 3.10 (m, 2H), 3.22 (m, 3H), 3.32 (m, 1H), 3.80 (s, 3H), 3.92 (m, 1H), 4.00-4.44 (m, 9H), 5.02 (s, 2H), 6.38 (s, 1H), 7.33 (d, 1H), 7.45 (m, 2H), 11.50 (bs, 1H). LRMS (ES$^+$): m/z (MH^+) 447 Microanalysis: Found: C, 59.36; H, 6.28; N, 10.53. $C_{28}H_{30}N_4O_3$;2HCl;0.4H_2O requires C, 59.29; H, 6.28; N, 10.64 %.

Ex. no.	R	Base	Yield/ Form	Spectroscopic and Analytical data
37 (b)		B	92	^{1}H-nmr (DMSO-d_6, 400MHz) δ: 0.71 (m, 2H), 0.97 (m, 2H), 3.26 (t, 2H), 3.38 (m, 1H), 3.74 (s, 3H), 4.12 (t, 2H), 5.08 (s, 2H), 6.35 (s, 1H), 7.07 (bs, 1H), 7.75 (dd, 1H), 8.20 (m, 1H), 8.66 (d, 1H). LRMS m/z: (ES^-) 347 ($M-H^-$)
38 (a)		A	42 white solid	^{1}H-nmr (DMSO-d_6, 400MHz) δ: 0.72 (m, 2H), 0.99 (m, 2H), 1.97 (m, 4H), 3.00 (m, 2H), 3.26-3.46 (m, 5H), 3.80 (s, 3H), 4.17 (m, 2H), 4.61 (s, 2H), 5.12 (s, 2H), 6.38 (s, 1H), 7.28 (bs, 1H), 7.57 (bs, 1H), 8.46 (d, 1H), 10.56 (bs, 1H). LRMS m/z : (ES^+) 432 (MH^+)
39		A	71 white solid	^{1}H-nmr (DMSO-d_6, 400MHz) δ: 0.74 (m, 2H), 0.97 (m, 2H), 1.55 (m, 2H), 1.82 (m, 4H), 3.03 (t, 2H), 3.16-3.38 (m, 5H), 3.80 (s, 3H), 4.16 (t, 2H), 4.50 (s, 2H), 5.17 (s, 2H), 6.38 (s, 1H), 7.32 (d, 1H), 7.62 (bs, 1H), 8.49 (d, 1H), 10.04 (bs, 1H). LRMS m/z : (ES^+) 446 (MH^+) Microanalysis found: C, 58.21; H, 6.58; N, 13.05. $C_{26}H_{31}N_5O_2$;2HCl;H_2O requires C, 58.32; H, 6.63; N, 12.79%.

(b)-5,6,7,8-tetrahydro-1,6-naphthyridine (Chem. Pharm. Bull. 32, 2522, 1984) was used as the amine

Example 40

5-Cyclopropyl-2-(2-[(dim thylamino)methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-7-methoxy-4(3*H*)-quinazolinone dihydrochloride



A mixture of the chloride from preparation 18 (60mg, 0.24mmol), the amin hydrochloride from preparation 121 (80mg, 0.30mmol) and diisopropylethylamine (258mg, 2mmol) in n-butanol (4mL) was heated under reflux for 1.5 hours. The cooled mixture was poured into water and extracted with dichloromethane (3x50mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 80:20). The product was re-dissolved in dichloromethane treated with 1N ethereal hydrochloric acid (2mL), and the solution evaporated under reduced pressure to afford the title compound as a light brown solid, 60mg.

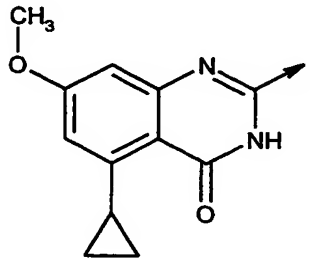
^{1}H-nmr (DMSO-d_6 400MHz): δ 0.72 (m, 2H), 0.97 (m, 2H), 2.87 (s, 6H), 3.14 (m, 2H), 3.36 (m, 1H), 3.79 (s, 3H), 4.18 (m, 2H), 4.56 (s, 2H), 5.13 (s, 2H), 6.38 (s, 1H), 7.42 (bs, 1H), 8.71 (s, 1H), 10.49 (bs, 1H).

LRMS : m/z (ES^+) 407 [MH^+]

Microanalysis: Found: C, 54.11; H, 5.94; N, 16.83. $C_{22}H_{26}N_6O_2$;2HCl;0.5H_2O requires C,54.10 ; H, 5.98; N, 17.21 %

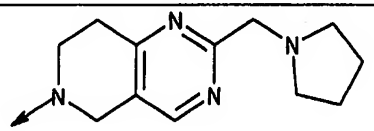
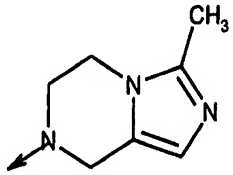
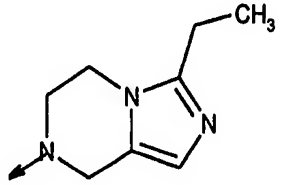
Examples 41 to 43

Th_ following examples of general structure:

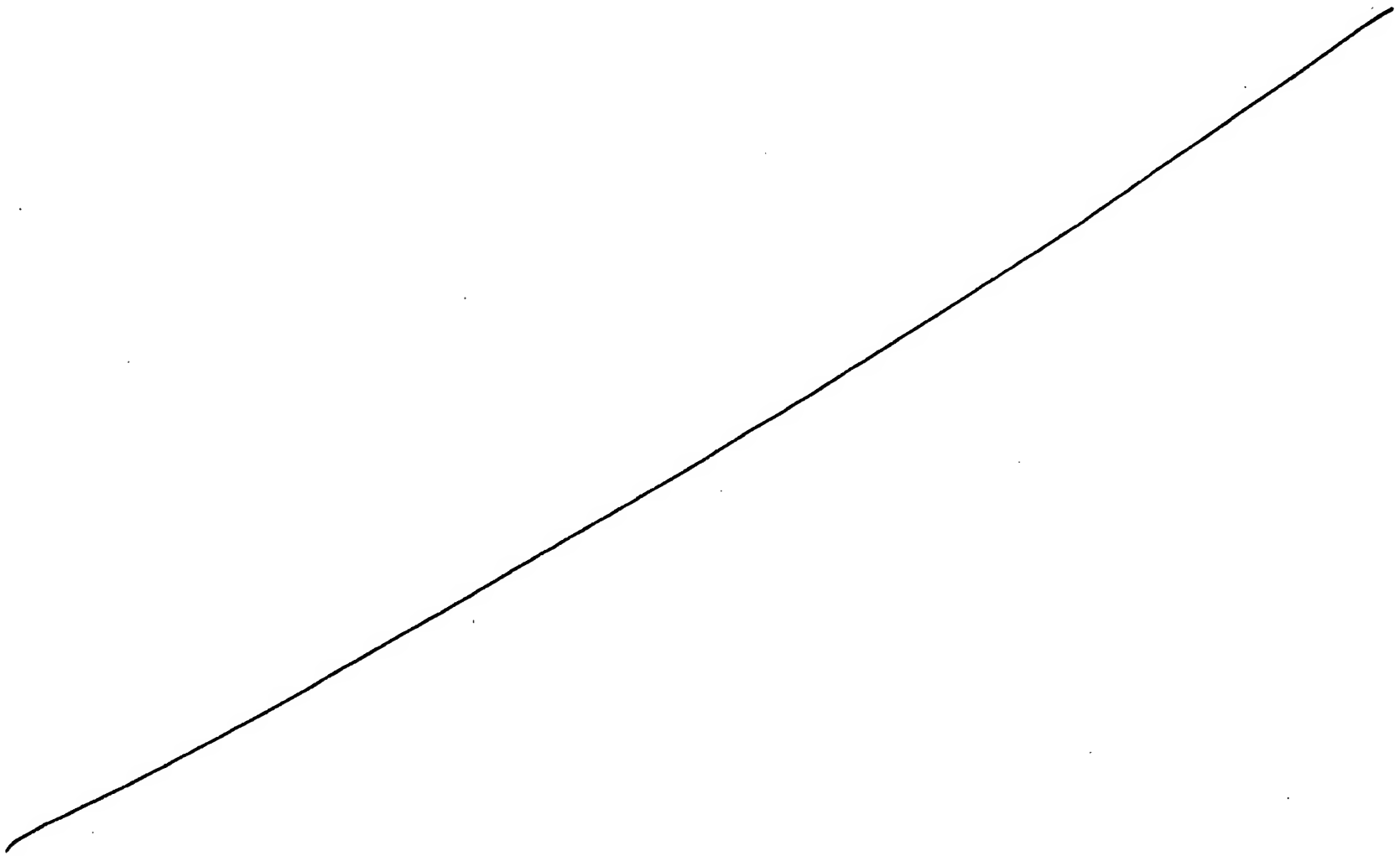


2HCl

were prepared from the chloride from preparation 18, the appropriate amines and diisopropylethylamine, following a similar procedure to that described in example 40.

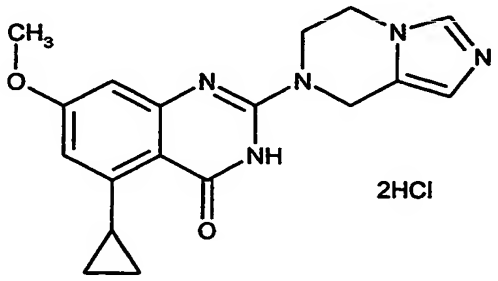
Ex. no.	R	Yield/ Form	Spectroscopic and Analytical data
41		63 off-white solid	^{1}H-nmr ($DMSOd_6$, 400MHz) δ : 0.68 (m, 2H), 0.95 (m, 2H), 1.85-2.05 (m, 4H), 3.05 (t, 2H), 3.15 (m, 2H), 3.43 (m, 1H), 3.60 (m, 2H), 3.75 (s, 3H), 4.05 (m, 2H), 4.65 (d, 2H), 4.95 (s, 2H), 6.25 (s, 1H), 6.85 (bs, 1H), 8.73 (s, 1H), 10.45 (bs, 1H). LRMS : m/z (ES$^+$) 433 [MH$^+$]
42 (a)		86 white solid	^{1}H-nmr (CD_3OD, 400MHz) δ : 0.77 (m, 2H), 1.07 (m, 2H), 2.66 (s, 3H), 3.10 (m, 1H), 3.91 (s, 3H), 4.34 (t, 2H), 4.43 (t, 2H), 5.16 (s, 2H), 6.64 (d, 1H), 7.11 (s, 1H), 7.46 (s, 1H). LRMS : m/z (ES$^+$) 352 [MH$^+$] Microanalysis: Found: C, 54.19; H, 5.77; N, 16.28. $C_{19}H_{21}N_5O_2$;2HCl requires C, 53.78 ; H, 5.46; N, 16.50 %
43 (a)		78 yellow foam	^{1}H-nmr (CD_3OD, 400MHz) δ : 0.78 (m, 2H), 1.09 (m, 2H), 1.41 (t, 3H), 3.04 (m, 3H), 3.92 (s, 3H), 4.35 (t, 2H), 4.46 (t, 2H), 5.18 (s, 2H), 6.65 (s, 1H), 7.12 (s, 1H), 7.49 (s, 1H). LRMS : m/z (ES$^+$) 366 [MH$^+$] Microanalysis: Found: C, 53.58; H, 5.97; N, 15.27. $C_{20}H_{23}N_5O_2$;2HCl requires C, 53.48 ; H, 5.88; N, 15.59 %

(a)-triethylamine was used instead of diisopropylethylamine



Example 44

5-Cyclopropyl-2-(5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-7-methoxy-4(3*H*)-quinazolinone dihydrochlorid



A mixture of the chloride from preparation 18 (70mg, 0.28mmol), the amine hydrochloride from preparation 129 (66mg, 0.34mmol) and triethylamine (113µl, 1.12mmol) in n-butanol (6mL) was heated under reflux for 6 hours. The cooled mixture was concentrated under reduced pressure and the residual solid partitioned between water (5mL) and dichloromethane:methanol (95:5, 50mL) and the layers separated. The aqueous phase was extracted with dichloromethane:methanol (95:5, 2x30mL), and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 90:10) to give a white solid. This was suspended in water, diluted with saturated sodium bicarbonate solution, and extracted with dichloromethane (3x50mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The solid was dissolved in dichloromethane:methanol (1:1, 8mL), 1N ethereal hydrochloric acid added, and the mixture evaporated under reduced pressure to afford the title compound as a foam, 69mg.

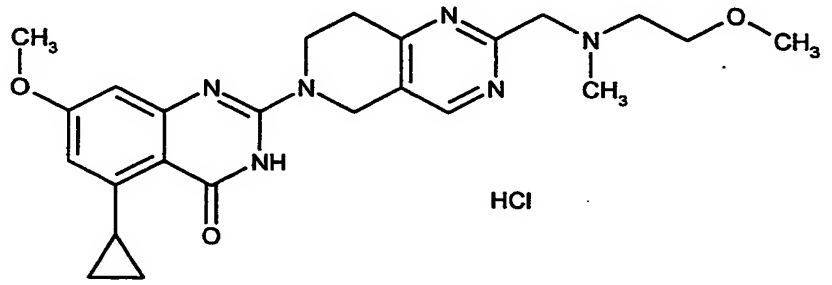
^{1}H-nmr ($DMSOd_6$, 400MHz) δ: 0.74 (m, 2H), 0.99 (m, 2H), 3.25 (m, 1H), 3.81 (s, 3H), 4.20 (t, 2H), 4.46 (t, 2H), 5.10 (s, 2H), 6.42 (s, 1H), 7.01 (s, 1H), 7.64 (s, 1H), 9.15 (s, 1H).

LRMS : m/z (ES^+) 338 [MH^+]

Microanalysis found: C, 52.78; H, 5.46; N, 16.82. $C_{18}H_{19}N_5O_2$;2HCl requires C, 52.69; H, 5.16; N, 17.07%.

Example 45

5-Cyclopropyl-7-methoxy-2-(2-{[(2-methoxyethyl)(methyl)amino]methyl}-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-4(3*H*)-quinazolinone hydrochloride



A mixture of the chloride from preparation 18 (140mg, 0.5mmol), the amine hydrochloride from preparation 122 (290mg, 0.84mmol) and triethylamine (390µl, 2.8mmol) in n-butanol (3mL) was heated under reflux for 1.5 hours. The cooled mixture was filtered, the resulting solid washed with n-butanol and diethyl ether, then dried at 60°C *in vacuo*, to afford the title compound as a cream solid.

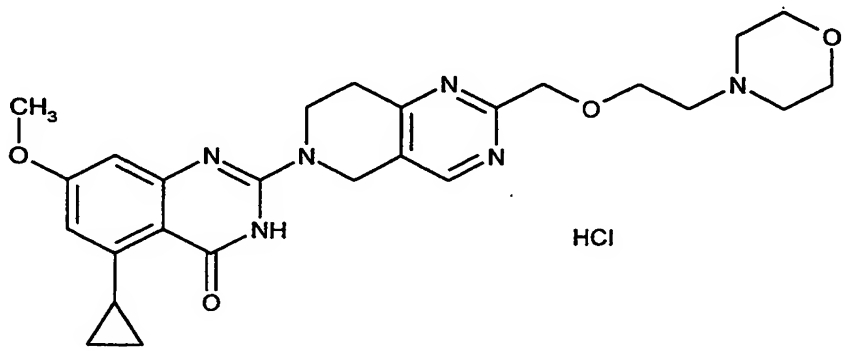
^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.73 (m, 2H), 0.97 (m, 2H), 2.41 (s, 3H), 2.75 (t, 2H), 3.08 (t, 2H), 3.33 (s, 3H), 3.38 (m, 1H), 3.56 (t, 2H), 3.86 (m, 5H), 4.10 (t, 2H), 4.92 (s, 2H), 6.33 (s, 1H), 6.68 (s, 1H), 8.51 (s, 1H), 11.12 (bs, 1H).

LRMS : m/z (ES^-) 449 [$M-H^-$]

Microanalysis found: C, 58.44; H, 6.16; N, 16.97. $C_{24}H_{30}N_6O_3$;HCl;0.3H_2O requires C, 58.54; H, 6.47; N, 17.07%.

Example 46

5-Cyclopropyl-7-methoxy-2-(2-{[2-(4-morpholinyl)ethoxy]methyl}-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-4(3*H*)-quinazolinone hydrochloride



The title compound was obtain d as a cream solid in 65% yield, from the chloride from preparation 18 and th amine hydrochloride from preparation 125, following a similar procedure to that describ d in xample 45, except, diisopropylethylamine was used instead of triethylamine.

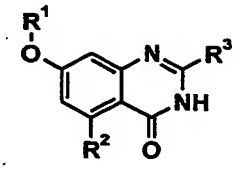
^{1}H-nmr ($CDCl_3$, 400MHz) δ: 0.85 (m, 2H), 00.97 (m, 2H), 2.50 (m, 4H), 2.67 (m, 2H), 3.09 (m, 2H), 3.38 (m, 1H), 3.65 (m, 4H), 3.74 (t, 2H), 3.83 (s, 3H), 4.15 (m, 2H), 4.72 (s, 2H), 4.91 (s, 2H), 6.35 (s, 1H), 6.64 (s, 1H), 8.53 (s, 1H), 10.88 (bs, 1H).

LRMS : m/z (ES^-) 491 [$M-H^-$]

Microanalysis found: C, 58.71; H, 6.15; N, 15.65. $C_{26}H_{32}N_6O_4$;HCl requires C, 59.03; H, 6.29; N, 15.89%.

Claims:

1. A compound of formula (I):



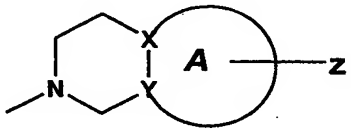
(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents C_{1-4} alkyl;

R^2 represents C_{3-6} cycloalkyl;

R^3 represents a bicyclic group of the formula



wherein X and Y are selected from C and N, provided that at least one is C;

Ring A together with X and Y represents a 5- or 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms in the ring;

Z is selected from H, and LR^4;

L represents a direct link, C_{1-4} alkylene or C_{1-4} alkoxyalkylene;

R^4 represents H, NR^5R^6, C_{3-6} cycloalkyl, OR^7 or Het^1;

R^5 and R^6 are independently selected from H, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with OR^8;

R^7 is selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{3-6}cycloalkyl, Het^2 and

C_{1-4}alkyl-Het^3;

R^8 is H or C_{1-4} alkyl;

Het^1, Het^2 and Het^3 independently represent a 4 to 7 membered saturated heterocyclic group which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, O or S, optionally substituted with OR^9 and/or C_{1-4} alkyl optionally substituted by OR^9;

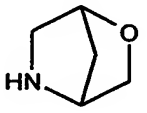
R^9 is H or C_{1-4} alkyl.

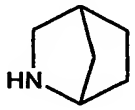
2. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein

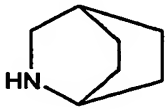
Het^1, Het^2 and Het^3 contain at least one N atom and are linked through an N atom.

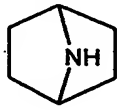
3. A compound of formula (I) according to claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein

Het^1, Het^2 and Het^3 include azetidine, pyrrolidine, piperidine, piperazine, azepane, morpholine, homomorpholine, or one of the following ring systems









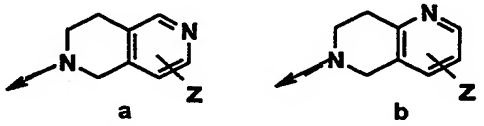
optionally substituted by OR^9, C_{1-4} alkyl optionally substituted by OR^9.

4. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is CH_3.

5. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is cyclopropyl.

6. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein L represents methylene.

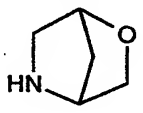
7. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 represents a group chosen from a or b (bonded to the quinazolinone through the N-atom as indicated)



where Z is CH_2Het^1 or $CH_2NR^5R^6$.

8. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 and R^6 are independently selected from H or C_{1-3} alkyl optionally substituted by OCH_3.

9. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein Het^1, Het^2 and Het^3 are selected from the group comprising pyrrolidine, piperidine, morpholine or



10. A compound of formula (I) as defined in claim 1 selected from:

5-cyclopropyl-7-methoxy-2-(2-([dimethylamino]methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(1-pyrrolidinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-([dimethylamino]methyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-pyrrolidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(1-piperidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-(4-morpholinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro[1,6]naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone;

and pharmaceutically acceptable salts or solvates thereof.

11. A pharmaceutical composition including a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.

12. A compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.

13. The use of a compound of the formula (I) as defined in claim 1, or of a pharmaceutically acceptable salt or solvate, in the manufacture of a medicament for the treatment of hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia.

14. The use according to claim 13, wherein the treatment is of benign prostatic hyperplasia.

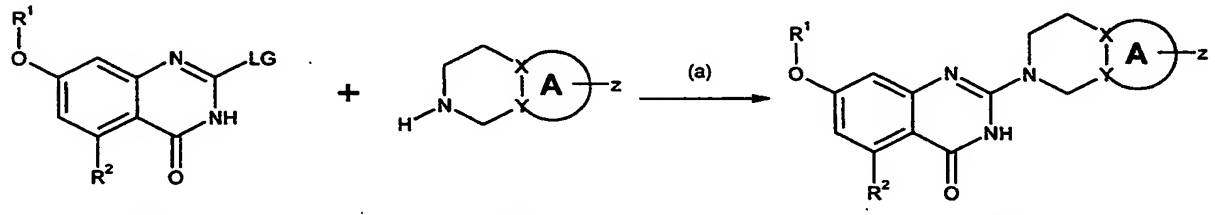
15. A method of treating hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia and. benign prostatic hyperplasia in a mammal, which comprises administering a therapeutically effective amount of a compound of the formula (I) as defined in claim 1, or with a pharmaceutically

acceptable salt, solvate or composition thereof, to a mammal in need of such treatment.

16. A method according to claim 15, for treating hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia.

17. A method according to claim 16, for treating benign prostatic hyperplasia.

18. A process for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, comprising reacting a quinazolinone (II) with an amine (III):



wherein R^1 and R^2 are as defined in claim 1 and LG represents a leaving group, and where desired or necessary converting the resulting compound of formula (I) into a pharmaceutically acceptable salt or solvate.

19. A compound of formula (II), as defined in claim 18.